Applications to Medical Imaging from diagnostic to therapy

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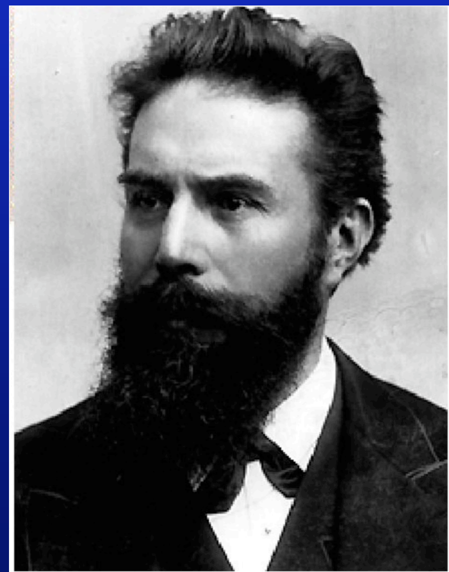
Protontherapy (PSI)

X-Rays, the fastest technology transfer example

- On November 8, 1895 Röntgen discovered X-Rays
- On November 22, 1895 he takes the first image of his wife's hand

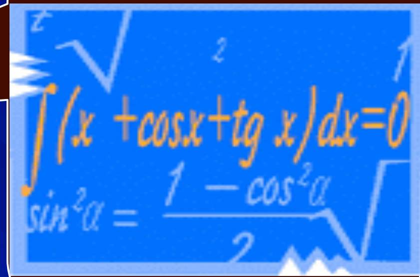


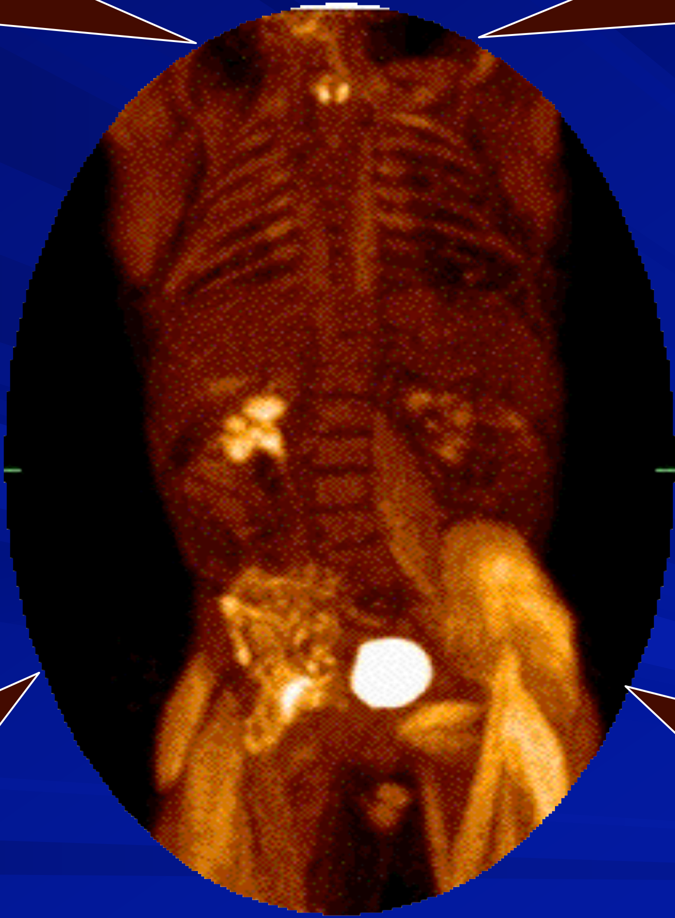
Röntgen received the <u>first</u> Nobel prize in <u>physics</u> in 1901

Medical Imaging: a multidisciplinary approach

Physics

Mathematics





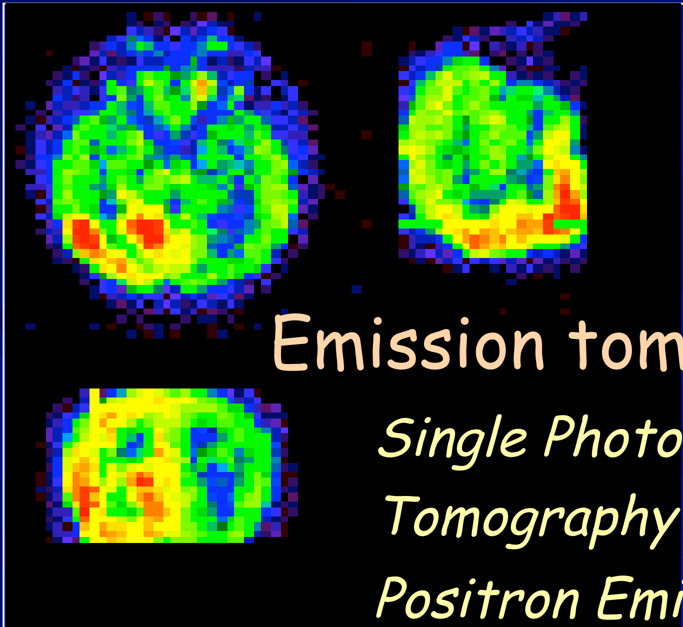
Medicine

Chemistry

Biology

Informatics

Medical Imaging Modalities



Emission tomography

Single Photon Emission Computerized Tomography (SPECT)

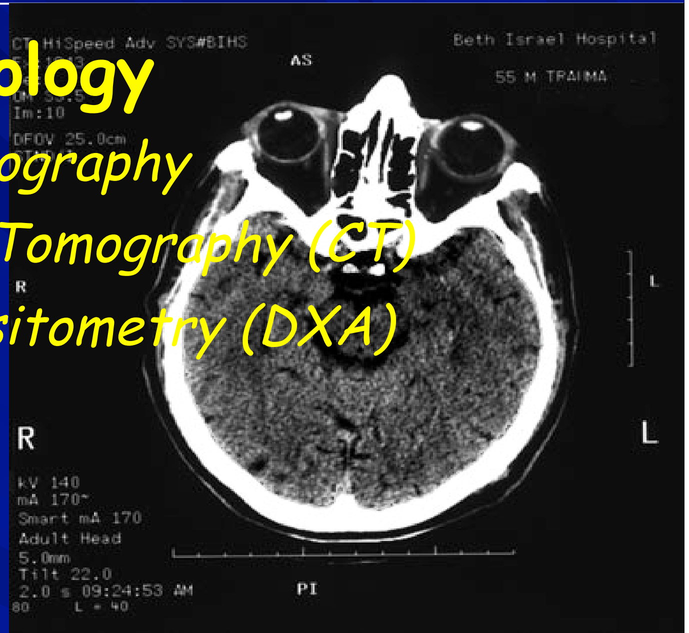
Positron Emission Tomography (PET)

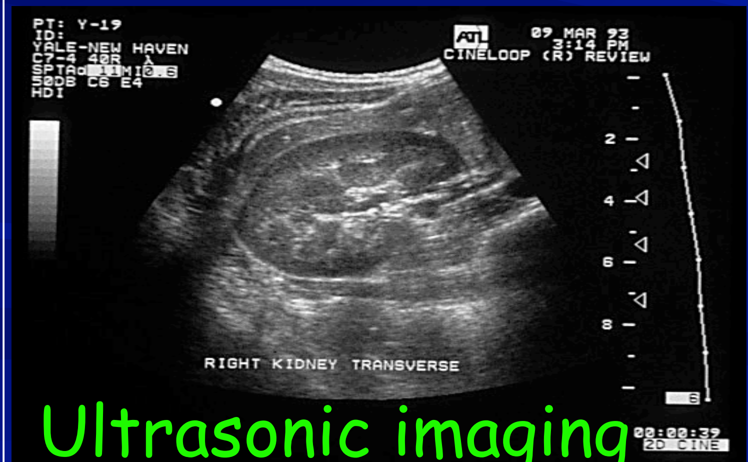
X-ray radiology

X-ray Radiography

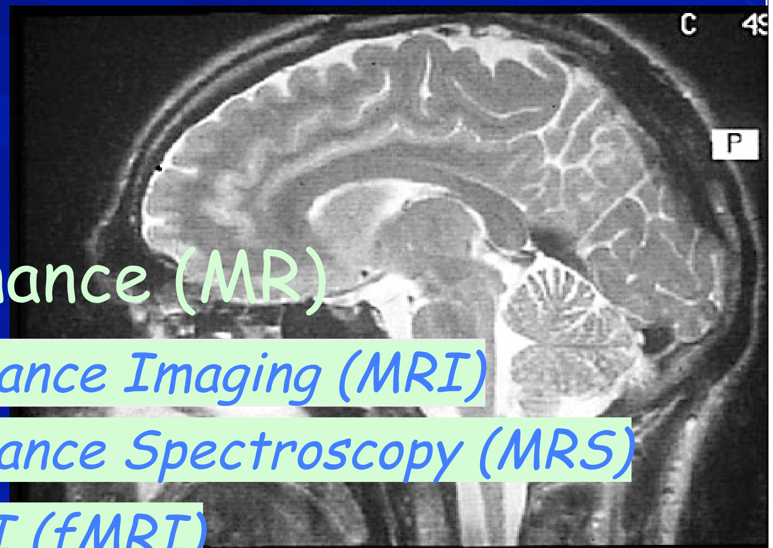
Computed Tomography (CT)

Tomo-Densitometry (DXA)





Ultrasonic imaging



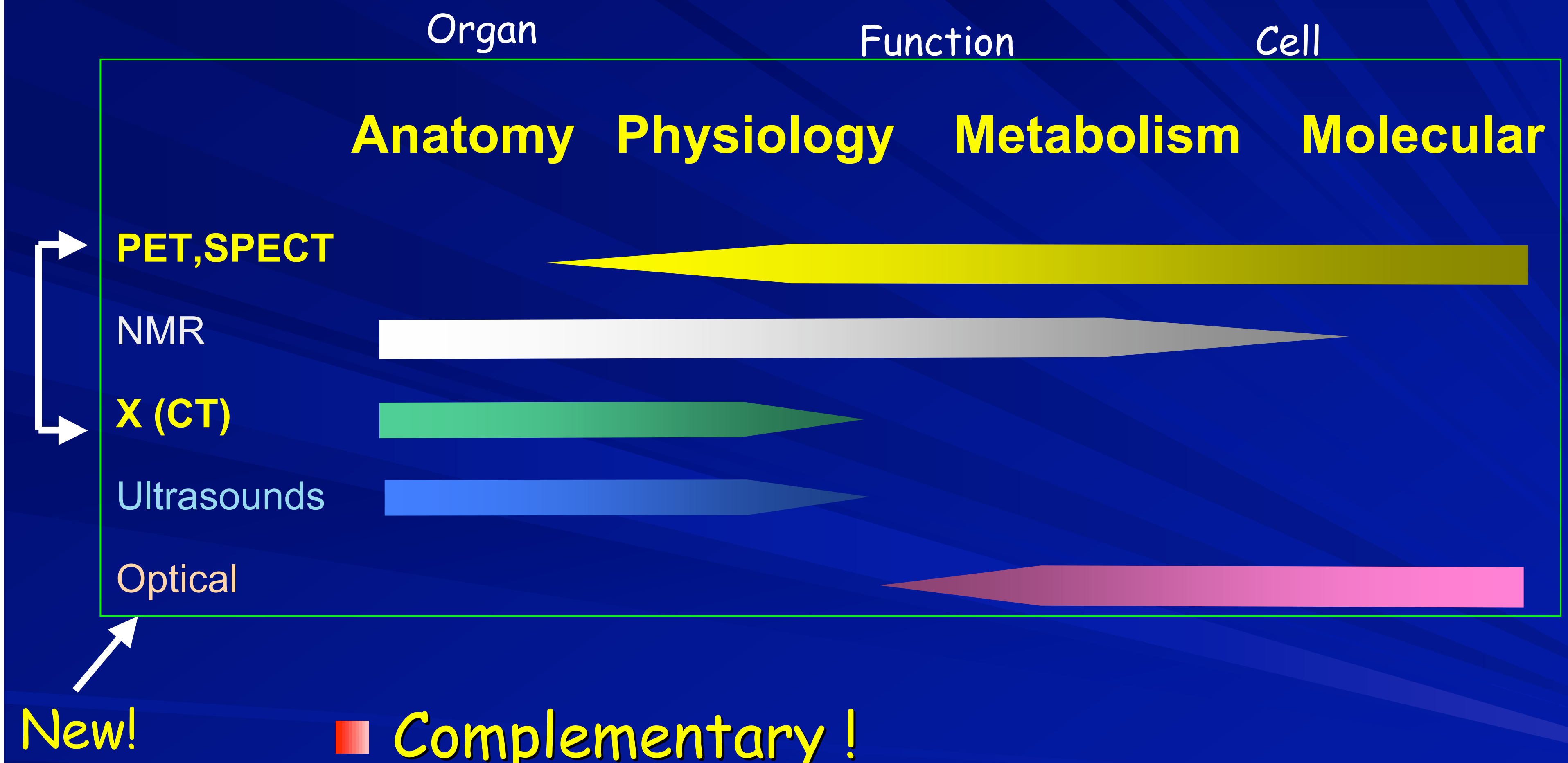
Magnetic Resonance (MR)

Magnetic Resonance Imaging (MRI)

Magnetic Resonance Spectroscopy (MRS)

Functionnal MRI (fMRI)

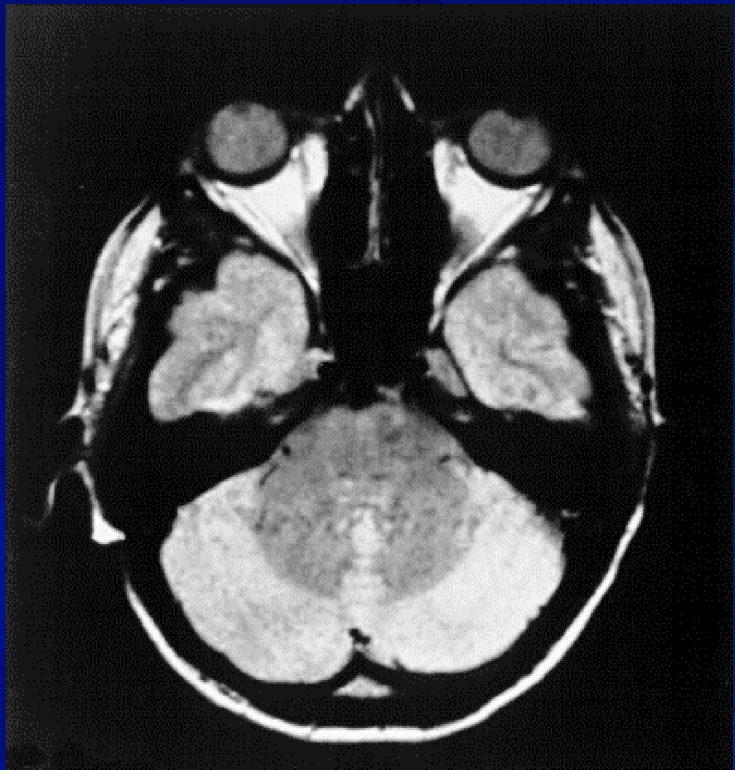
The various types of imaging

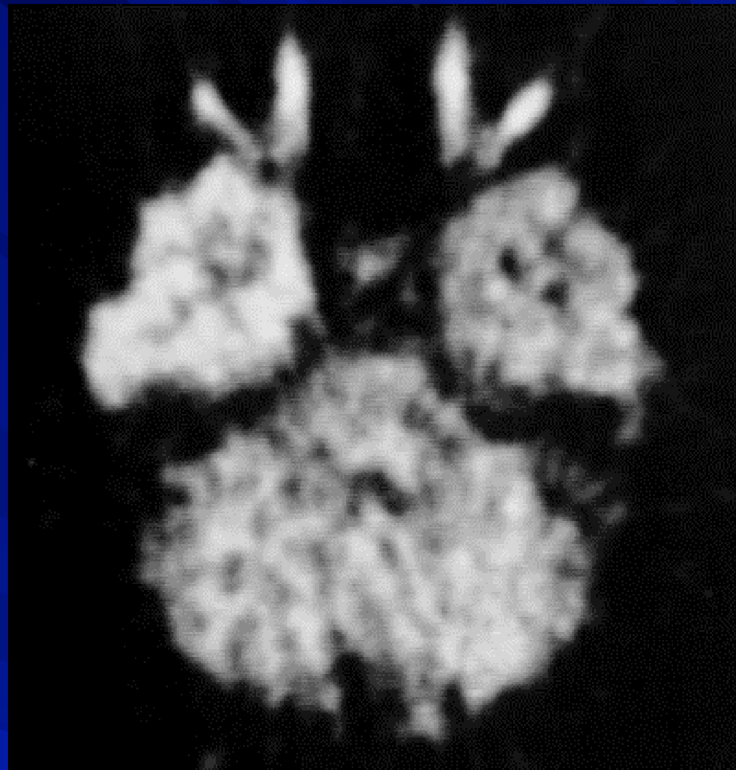


- Complementary !
- Depends on what you want to see

NMR & PET Images of Epilepsy

NMR



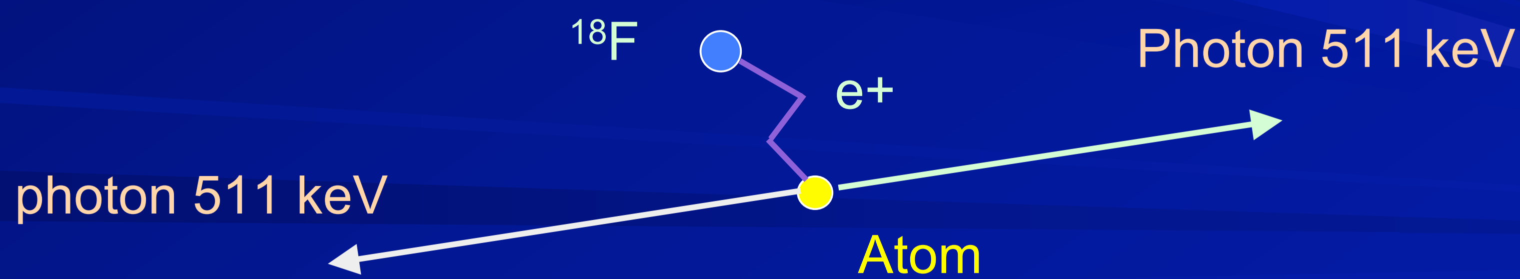


PET

- NMR "Sees" Structure with 0.5 mm Resolution
- PET "Sees" Metabolism with 5.0 mm Resolution but with very high sensitivity (picomolar level)

Positron Emission Tomography principle

- Functional imaging
- Molecular tracers with doped beta + emitters
  - ^{11}C(2à min), ^{15}O (2min) , ^{13}N (10 min),18F (2h)
  - Produced by a 18Mev Proton cyclotron
  - The most common → ^{18}F => ^{18}FDG fluoro-deoxy-glucose
    - Sign the degree of activity of an organ hungry of glucose
- annihilation positron with an electron
  - emission of two 511 keV photons back to back

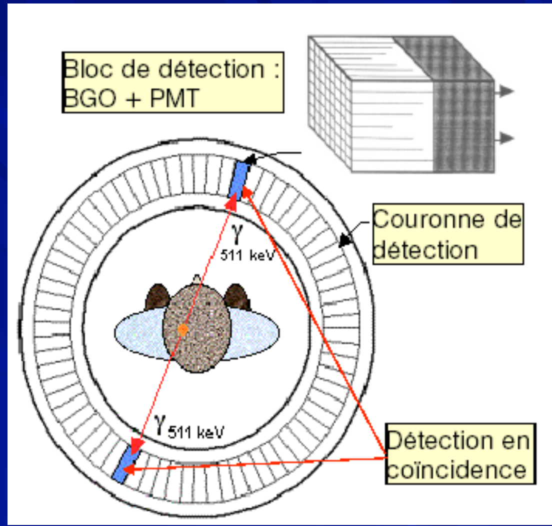


Physical constraints & limits

- **Emission**

  β+ flight path: ^{18}Fluor : E = 650 keV => <λ> = 2mm

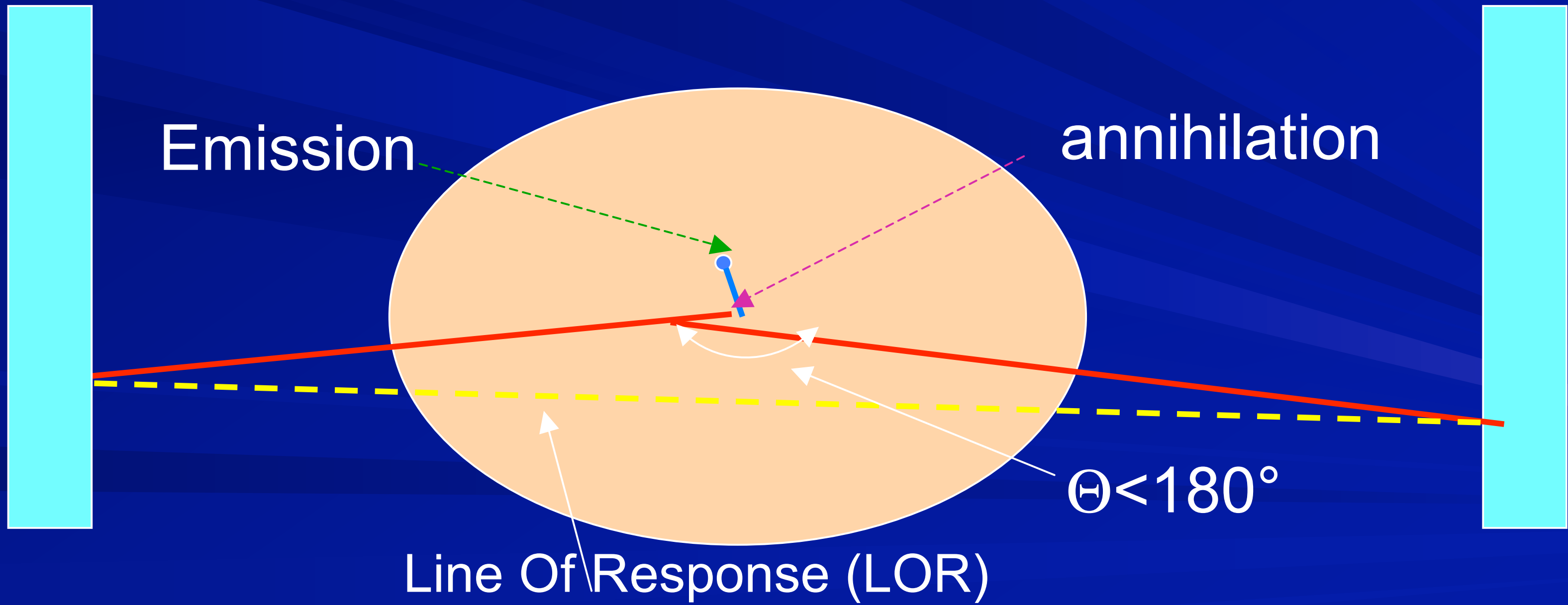
  accolinearity γ–γ : kinematic : <Θ>few mRad



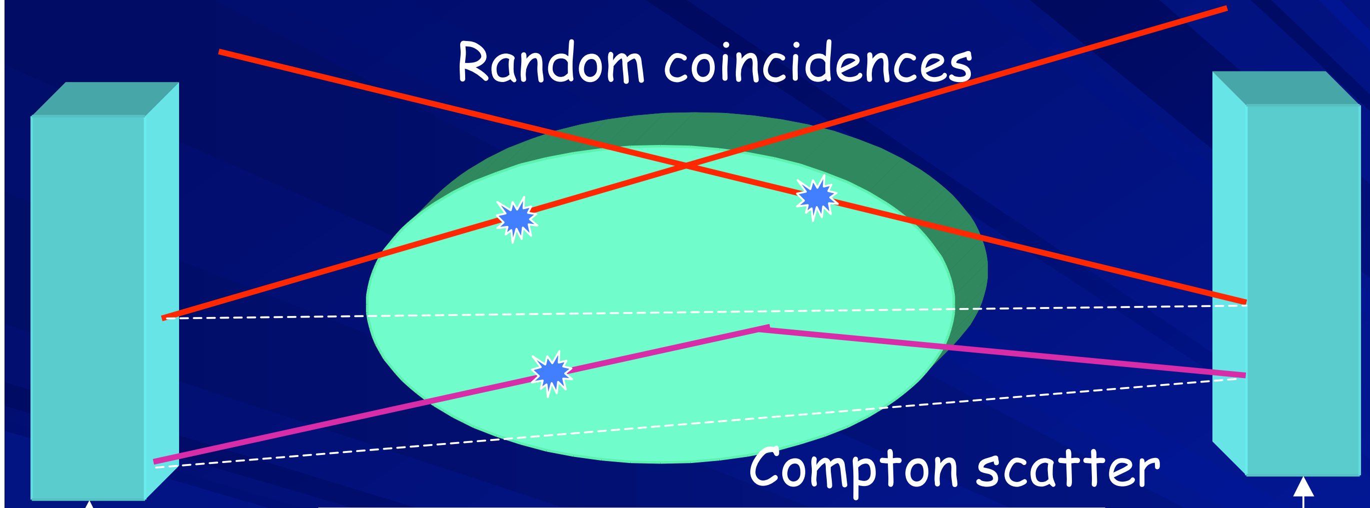
- **Detection**

  Detector resolution

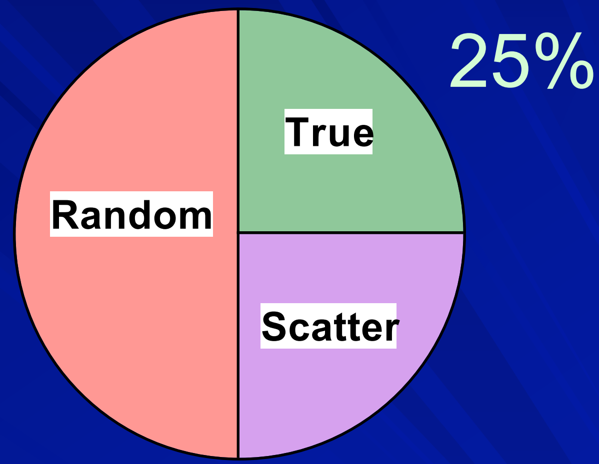
  Bias reconstruction

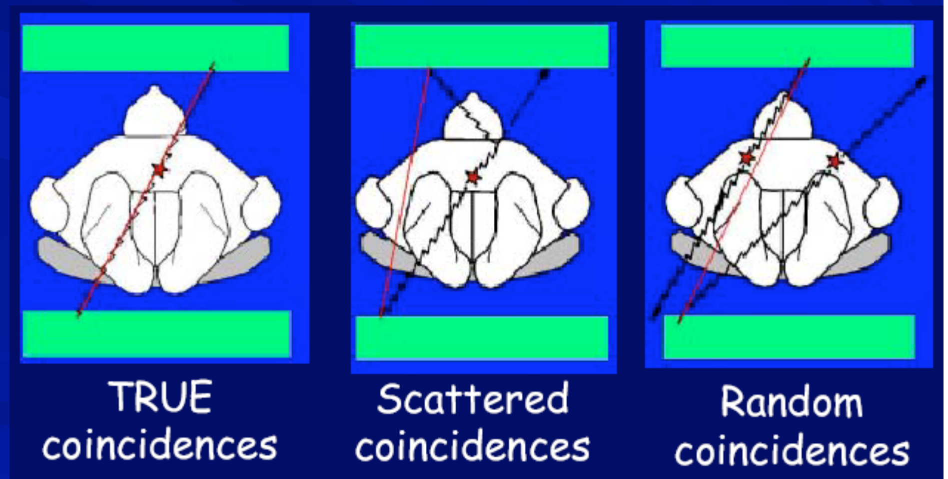


Source oF errors in the source



Dector in coincidences
Energy window around 511keV
Time window 10-20 ns

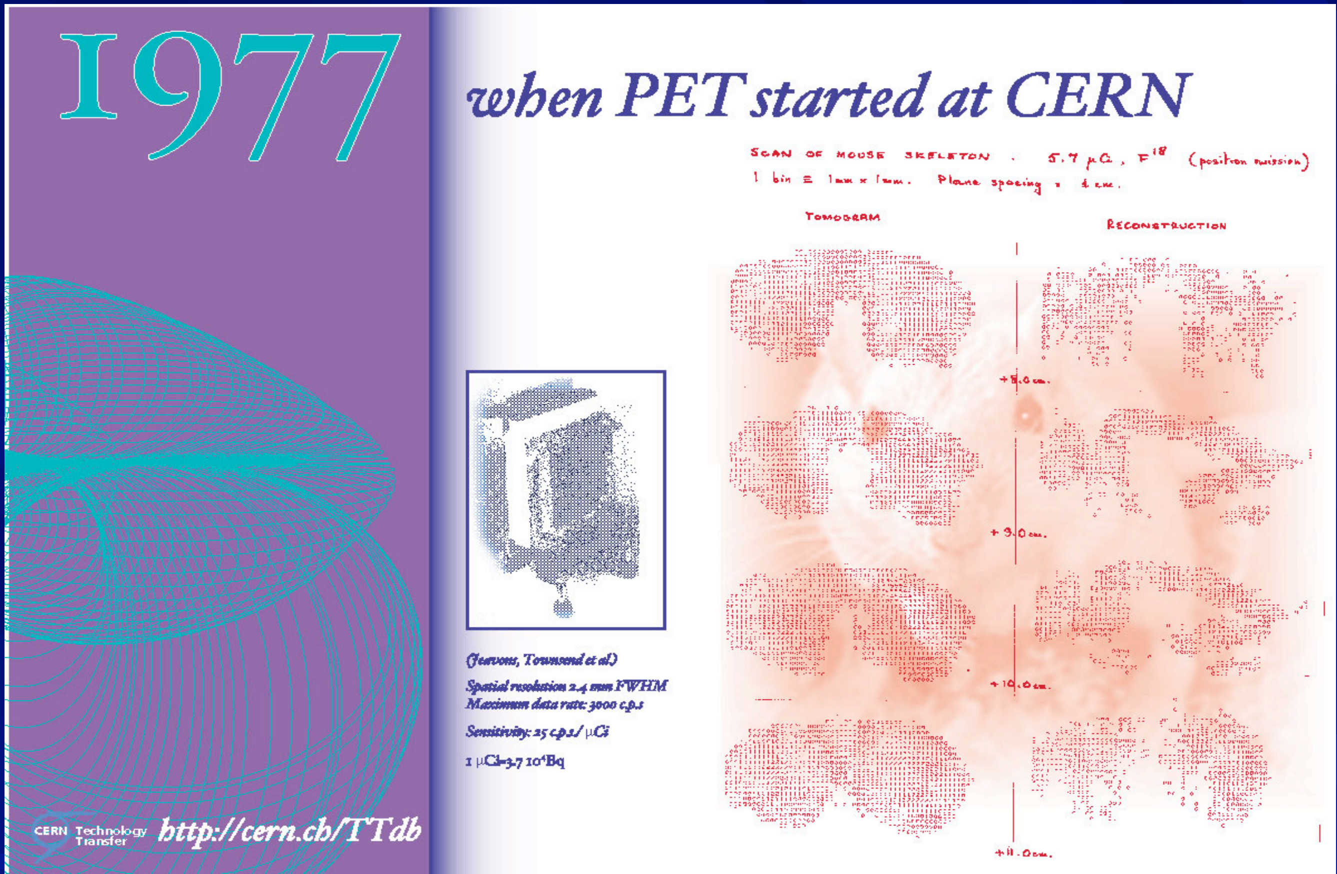




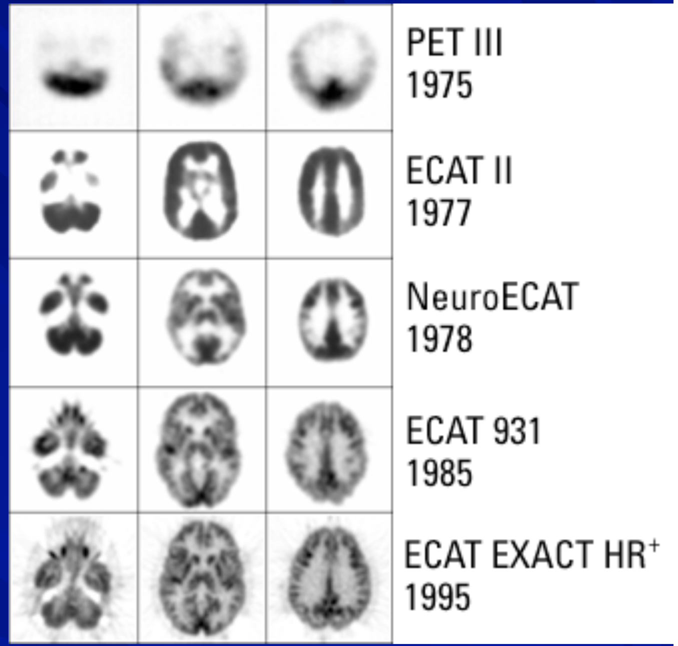
Signal : true concidences
Background: Compton + Random

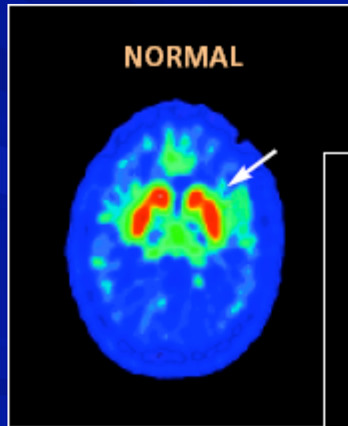
Efficiency ≈ 0,01
(1 photon / 100)

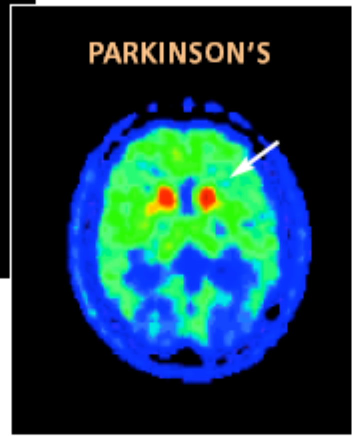
Some history



Jeavons,Townsend & al.





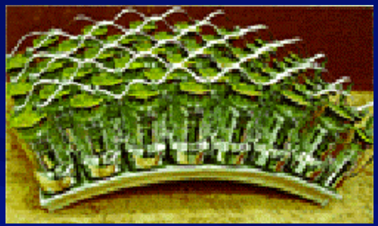


Today

Clinical PET Imaging

- Whole body PET PET → Φ=90cm- FOV 20 cm
  - Oncology → market increase 30% per year !

C-PET
Philips
1997

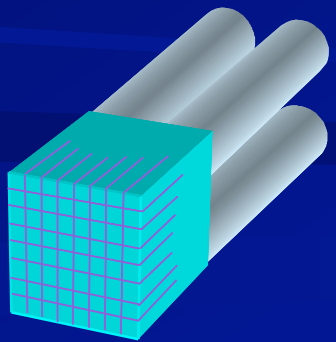


NaI curved
CPET (Philips)

CTI
Siemens
LSO

Patient treated for a colon cancer and revealing under PET/CT scan an additional breast cancer

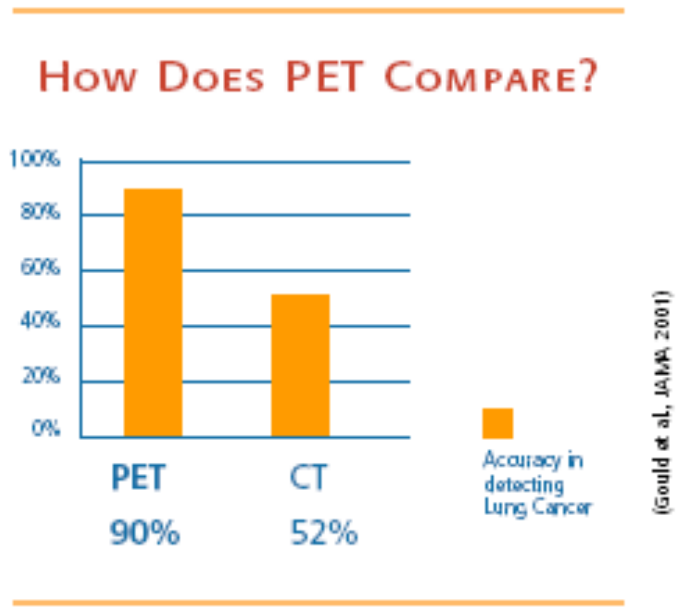
2006



Detection block
Crystals 4x4x20 (or 30) mm^3
Block 8 x 8 crystals , 2 x 2 PM's

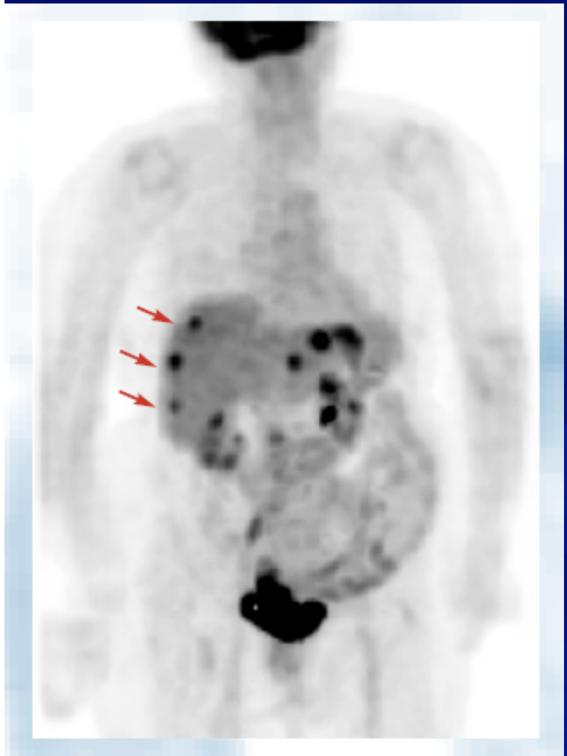
Medical PET examples : Lung Cancer

New Cases 185,800/yr
Deaths 163,700/yr



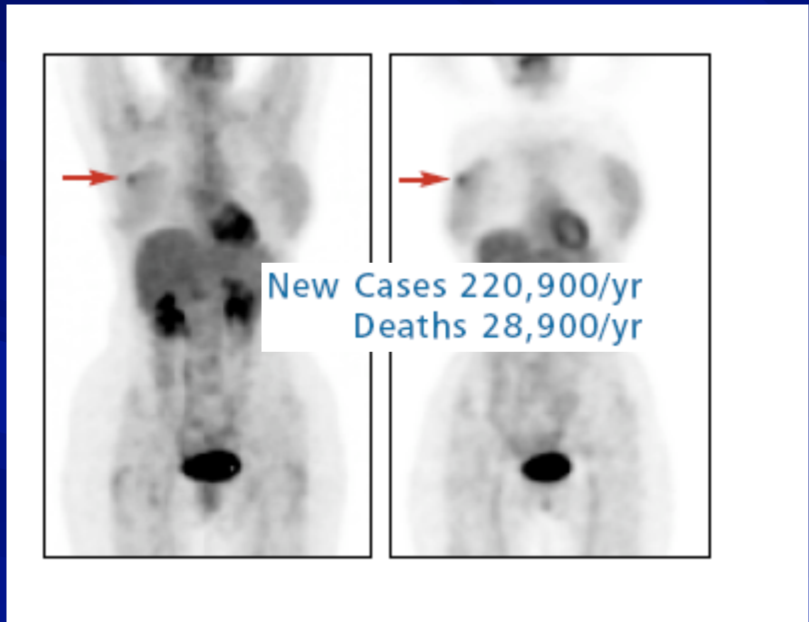
Others types of common cancers

Colon



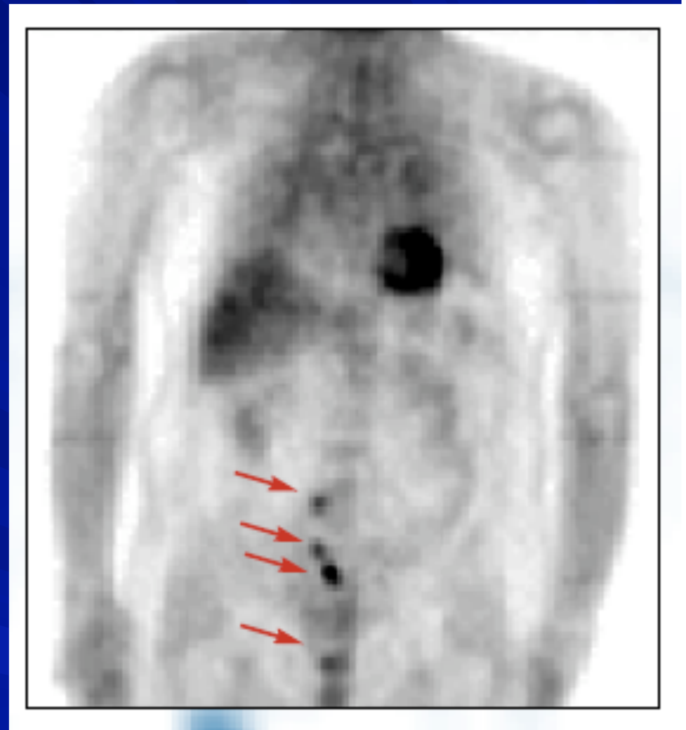
New Cases 147,500/yr
Deaths 57,100/yr

Breast



New Cases 212,600/yr
Deaths 40,200/yr

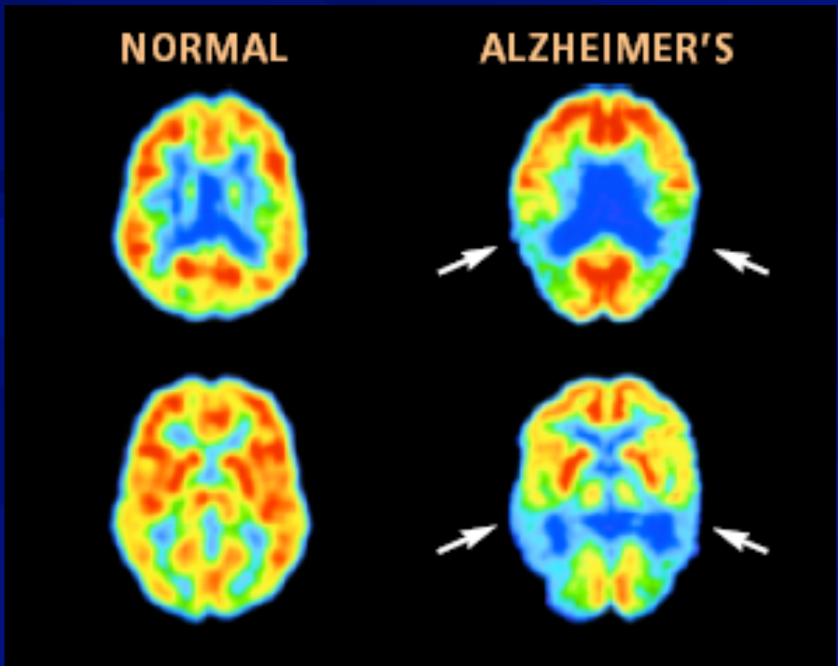
Prostate



New Cases 220,900/yr
Deaths 28,900/yr

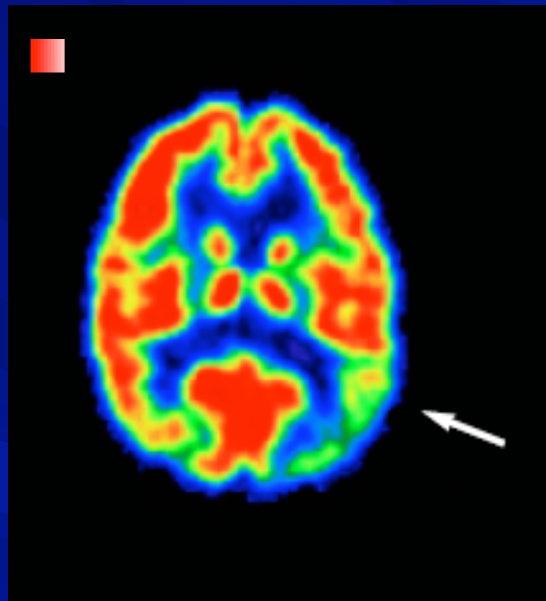
PET for brain diseases

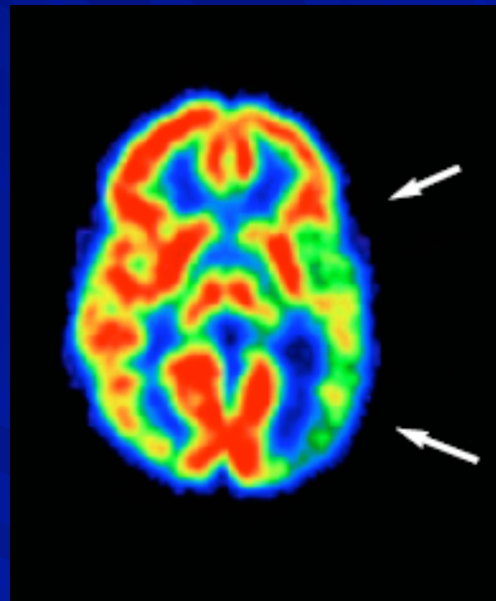
Alzheilmer



The PET shows decreased metabolism
early in the desease!

Parkinson





The PET scan showed abnormal glucose metabolism in the back of the right emisphere
Folloing surgical removal of the dysfonctional brain area the child was seizure free

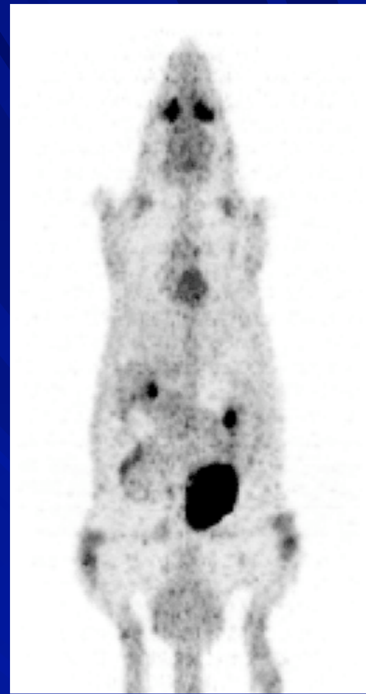
MicroPET → Φ=20cm- FOV few cm

- Radio pharmacology
- Tracer development

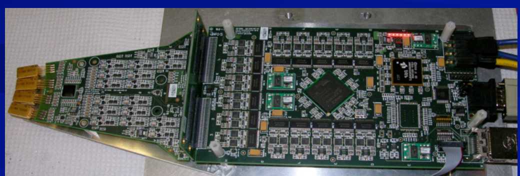
LabPET

ClearPET

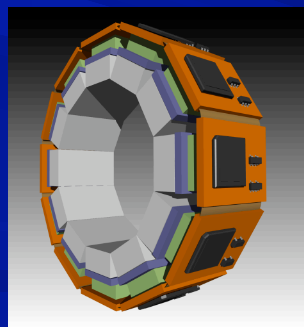
31 g mouse
1 mCi $^{18}F^{-}$



Whole-body
FDG-PET scan
250 g rat
(Sherbrooke APD)



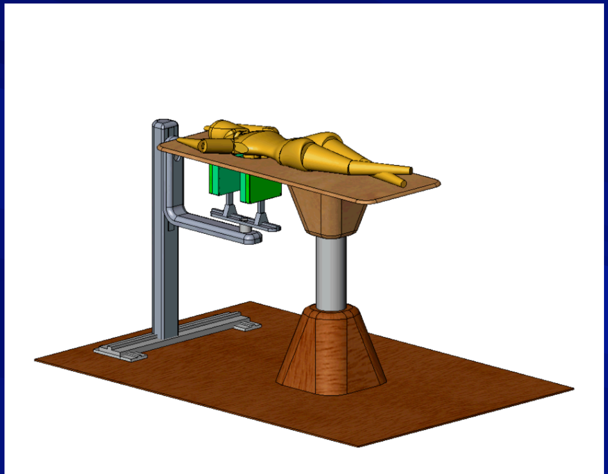
APD PET

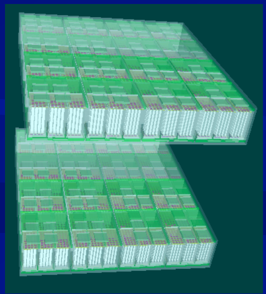


RatCap

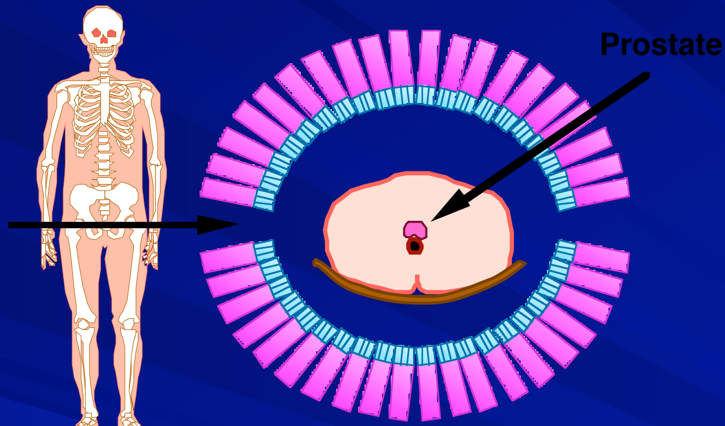
Dedicated PET

Mammography (CLEARPEM)

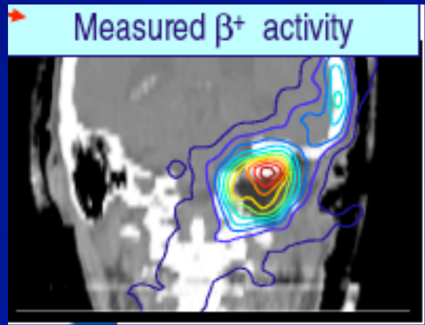


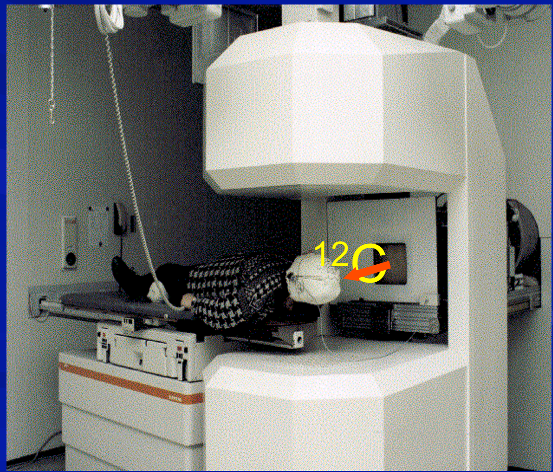


Prostate PET



On Line PET for hadrontherapy





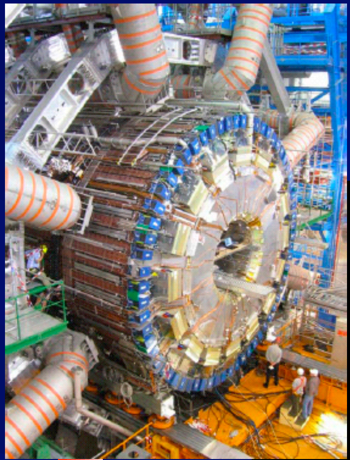
µPET vs whole body PET → different requirements

- High Spatial resolution
  →fundamental
  - Objective ~ 1mm or less
  - Today → 1,2 mm
- High sensitivity
  - Less Compton event
  - Small dose
- Paralax correction
  → Deph Of Interaction Technique

- High Efficiency (>85%)
- Good Spatial Resolution (<5 mm)
- Low Cost (<$100/cm2)
- Short Dead Time (<1 µs)
- High Timing Resolution (<5 ns fwhm)
- Good Energy Resolution (<100 keV fwhm)

Why PET ?

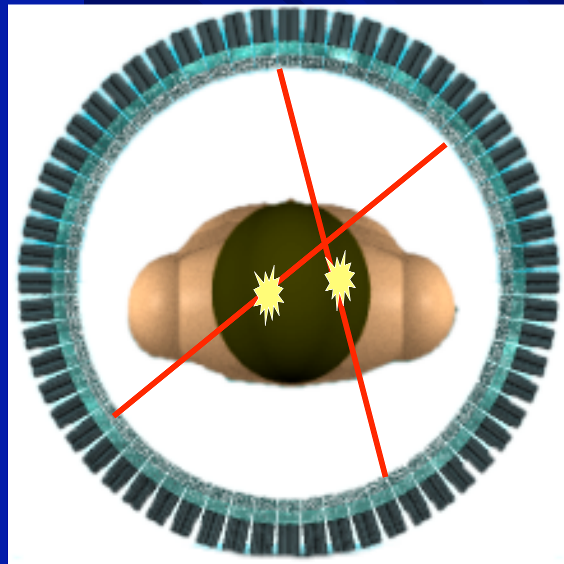
Similarities and differences

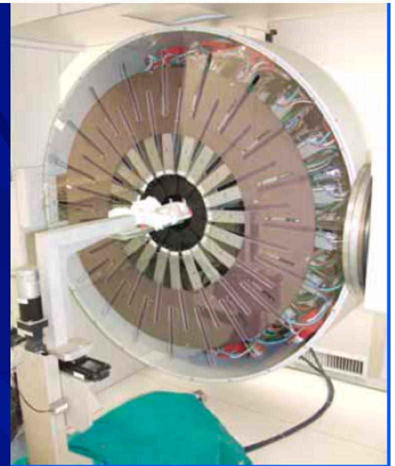


Calorimeter

HEP

M_{Higgs} = 100 GeV





PET Camera

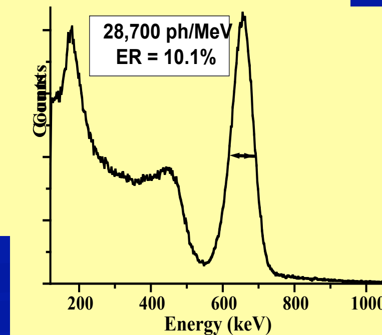
Biomedical Imaging

Similarities

- Geometry and granularity
- Detector (Crystals & scintillator)
- Sensor (PM,APD)
- Electronics:Fast (40 MHz), compact
- Event rate & Data volume (Gbit/s)

Differences

- Energy range (10GeV-511keV)
- No synchronisation --> free running electronics
- Multiple vertices



From HEP to Medical

Where ***techniques*** *are transfered to developments in bio- medical field*

Medical Imaging has only partially benefited from new technologies developed for telecommunications and High Energy Physics detectors

- **New scintillating crystals and detection materials →**
  - CMS (WPbO4) → Luap …(Crystal Clear col)
- Photodetectors : **Highly segmented and compact** → PMT → APD → SiPM
  - APD : SSC/SDC (1991) → CMS (1996) → MicroTEP→ TEP
- Electronics & signal treatemnt→ Highly integrated
  - Fast, low noise,low power preamp
  - Digital filtering and signal analysis
- Trigger/DAQ →
  - High level of parallelism and event filtering algorithms
  - Pipeline and parallel read-out, trigger and on-line treatment
- Computing
  - Modern and modular simulation software using worldwide recognized standards (GEANT)

From HEP detectors to Medical Imaging

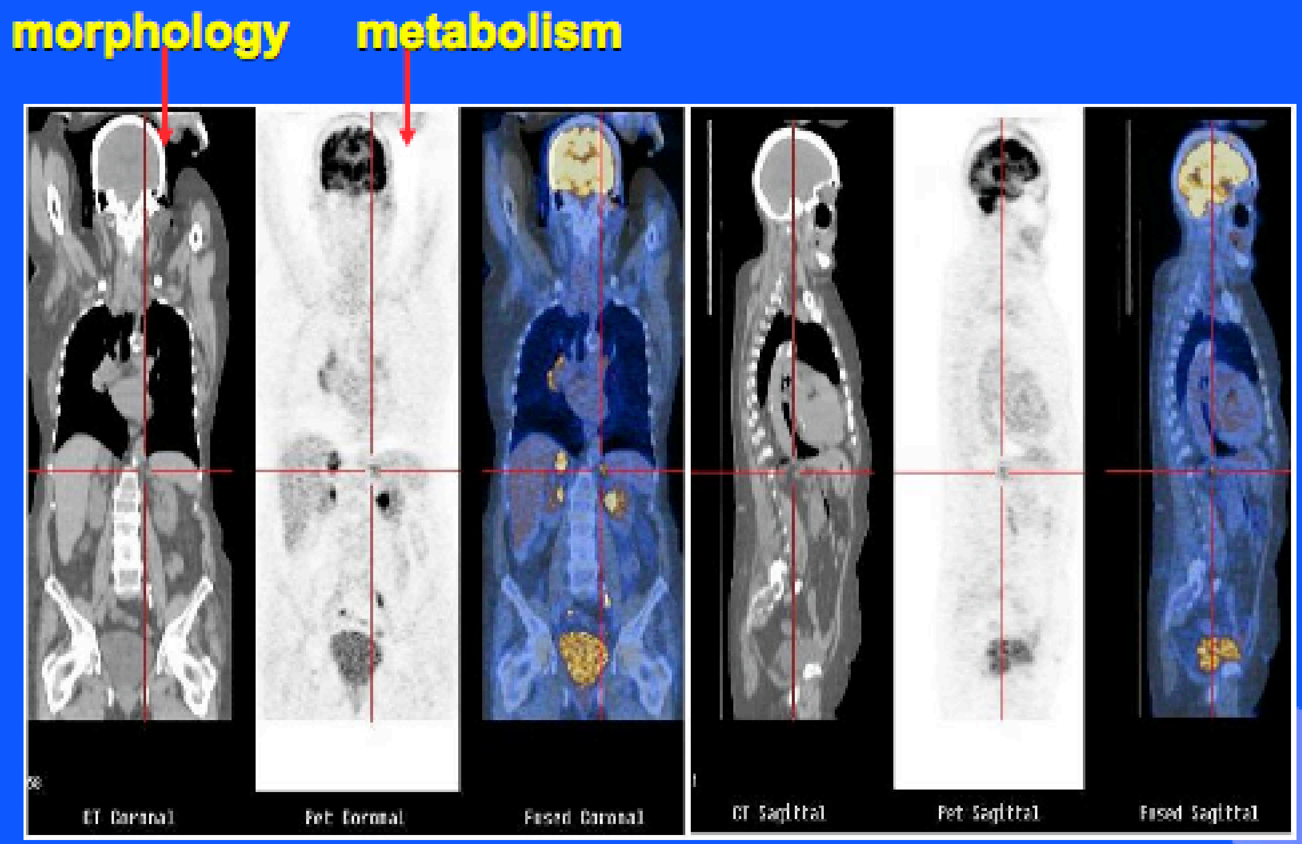
Requirements for HEP EM calorimetry

1. Crystals — Technology transfer
   - High density (> 6 g/cm^3)
   - Fast emission (< 100 ns), visible spectrum
   - Moderate to high light yield
   - High radiation resistance
2. Photodetectors — Technology transfer
   - Compact
   - High quantum efficiency and high gain
   - High stability
3. Readout electronics — Technology transfer
   - Fast shaping, low noise
   - Highly integrated
4. Intelligent and parallel DAQ — Technology transfer
   - Reduce dead time
5. Software — Technology transfer
   - Accurate Monte Carlo simulation
6. General design — Technology transfer
   - Compact integration of a large number of channels (> 10'000)

Requirements for Medical Imaging

1. Crystals
   - High density (> 7 g/cm^3)
   - Fast emission (< 100 ns), visible spectrum
   - High light yield
   - Moderate radiation resistance
2. Photodetectors
   - Compact
   - High quantum efficiency and high gain
   - High stability
3. Readout electronics
   - Fast shaping, low noise
   - Highly integrated
4. Intelligent and parallel DAQ
   - Reduce dead time
5. Software
   - Accurate Monte Carlo simulation
6. General design
   - Compact integration of a large number of channels (> 10'000)

The Present: Combine anatomic and fonctional informations



David Townsend

CERN: 1970-78

Université de Genève

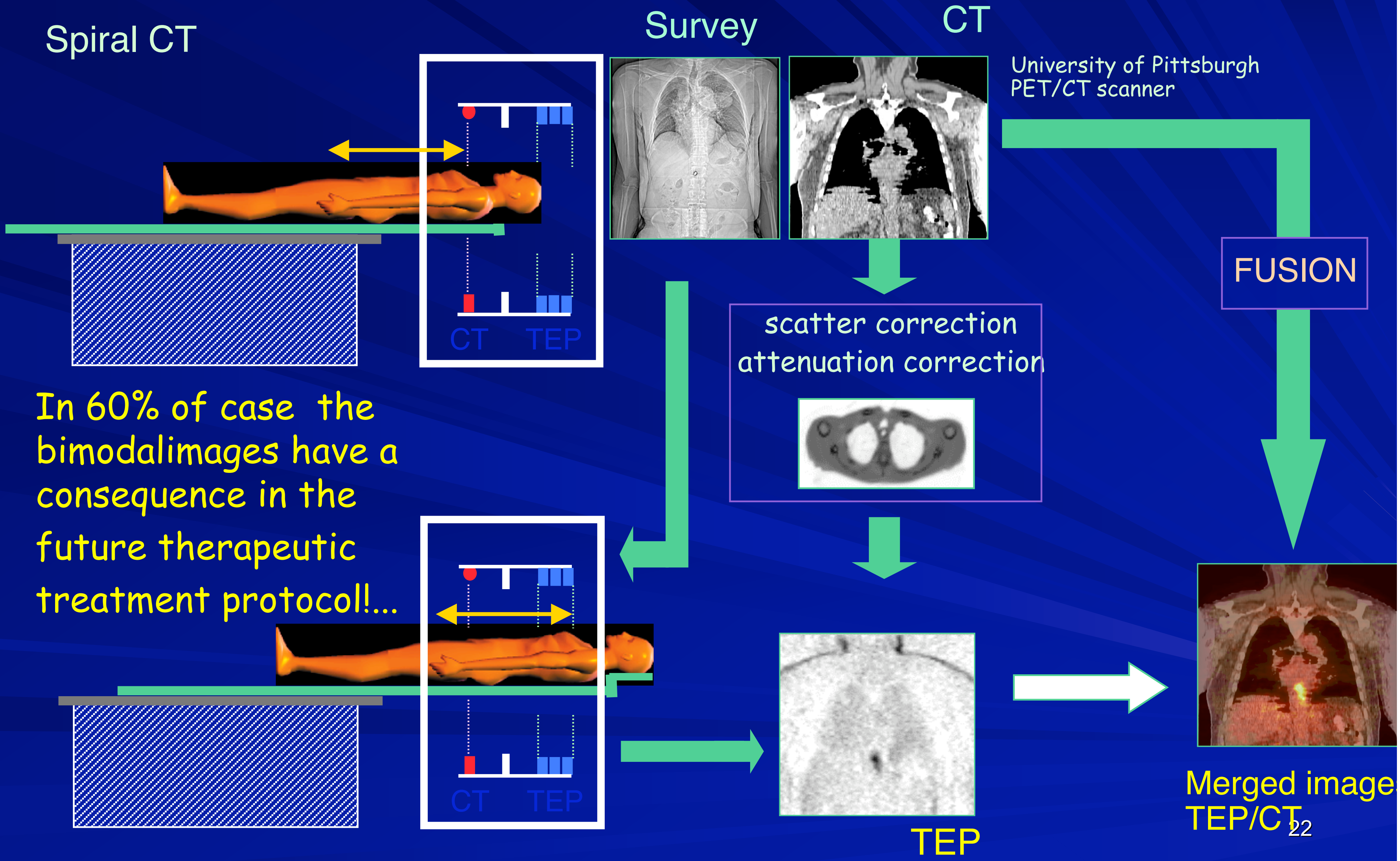
UPSM Pittsburgh

and

Ronald Nutt

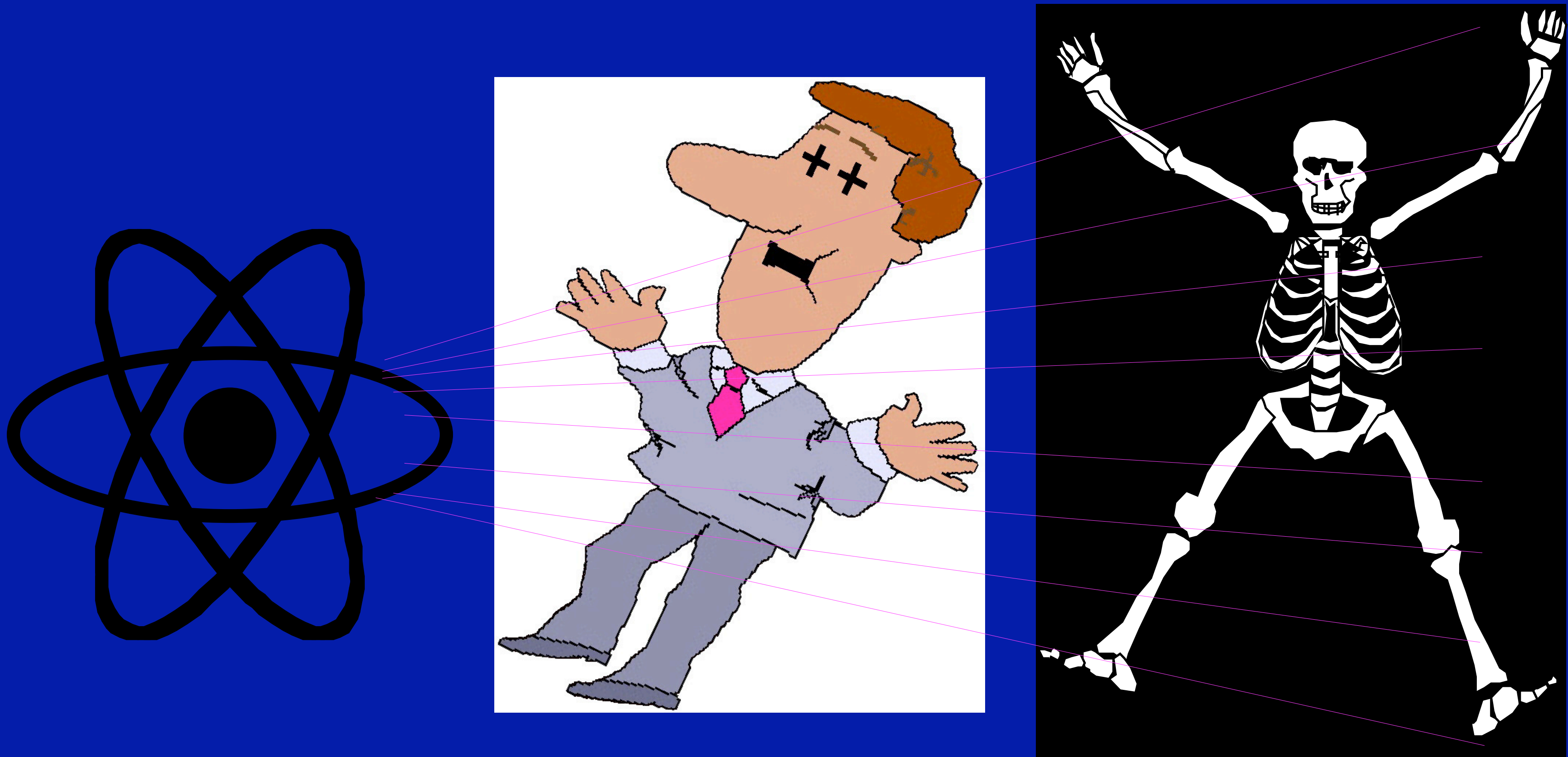
(CTS – CTI)

Today state of the art: TEP + CT



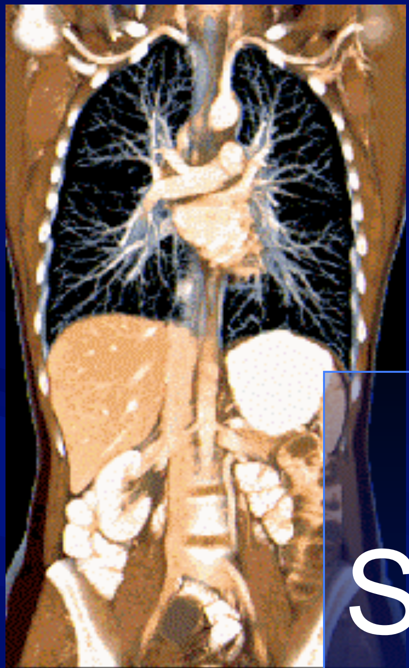
In 60% of case the bimodalimages have a consequence in the future therapeutic treatment protocol!...

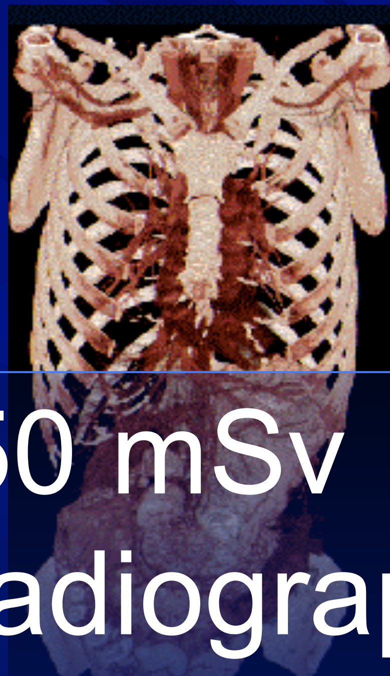
Patient Radiation Dose is Limited!



- Image Noise Is Limited by Counting Statistics
- Cannot Increase too much Source Strength

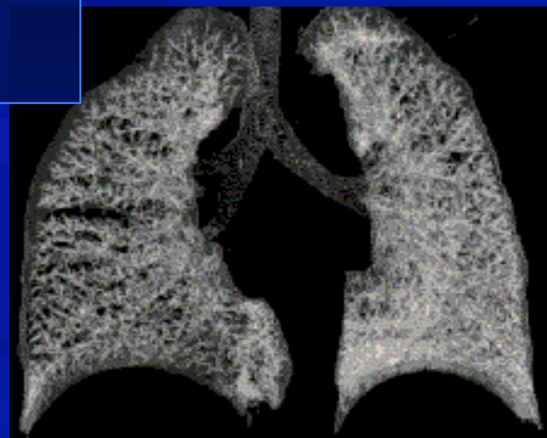
Volumetric CT





< 0,4 sec/ rotation
Organ in a sec (17 cm/sec)
Whole body < 10 sec

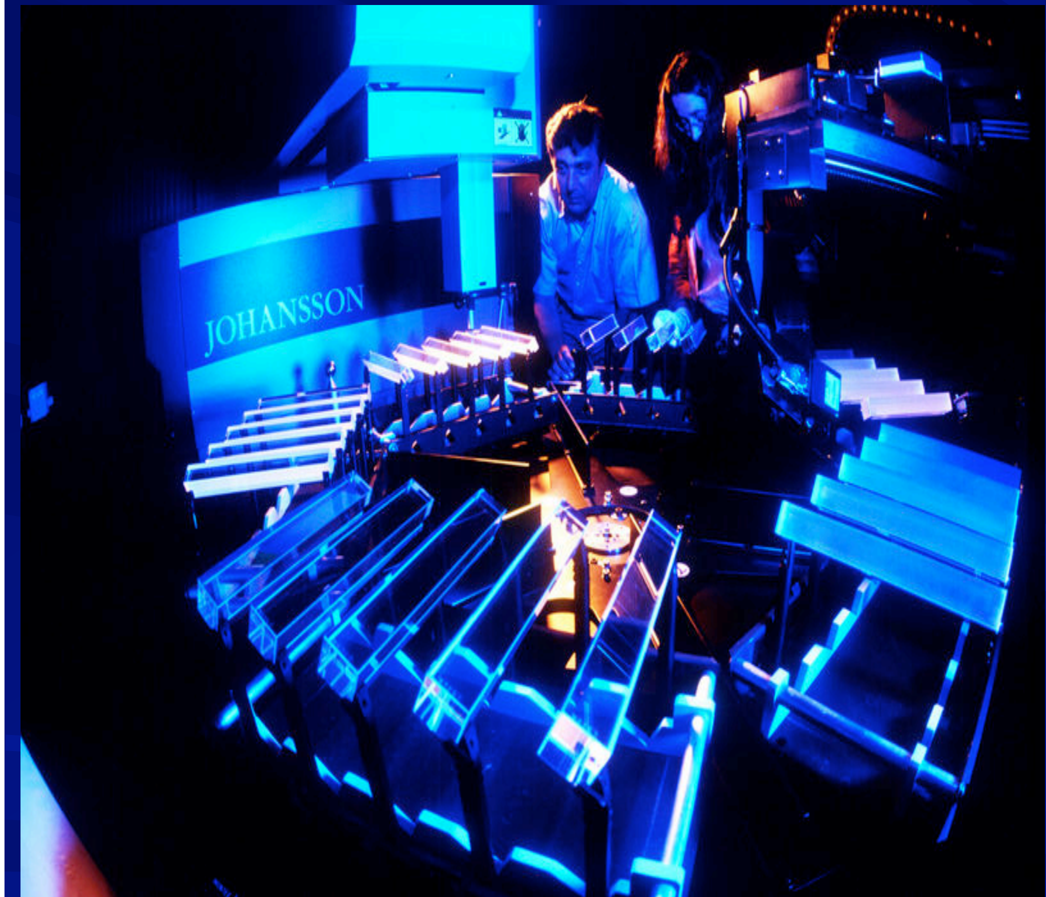
20 to 50 mSv
Standard radiography
0.1 mSv



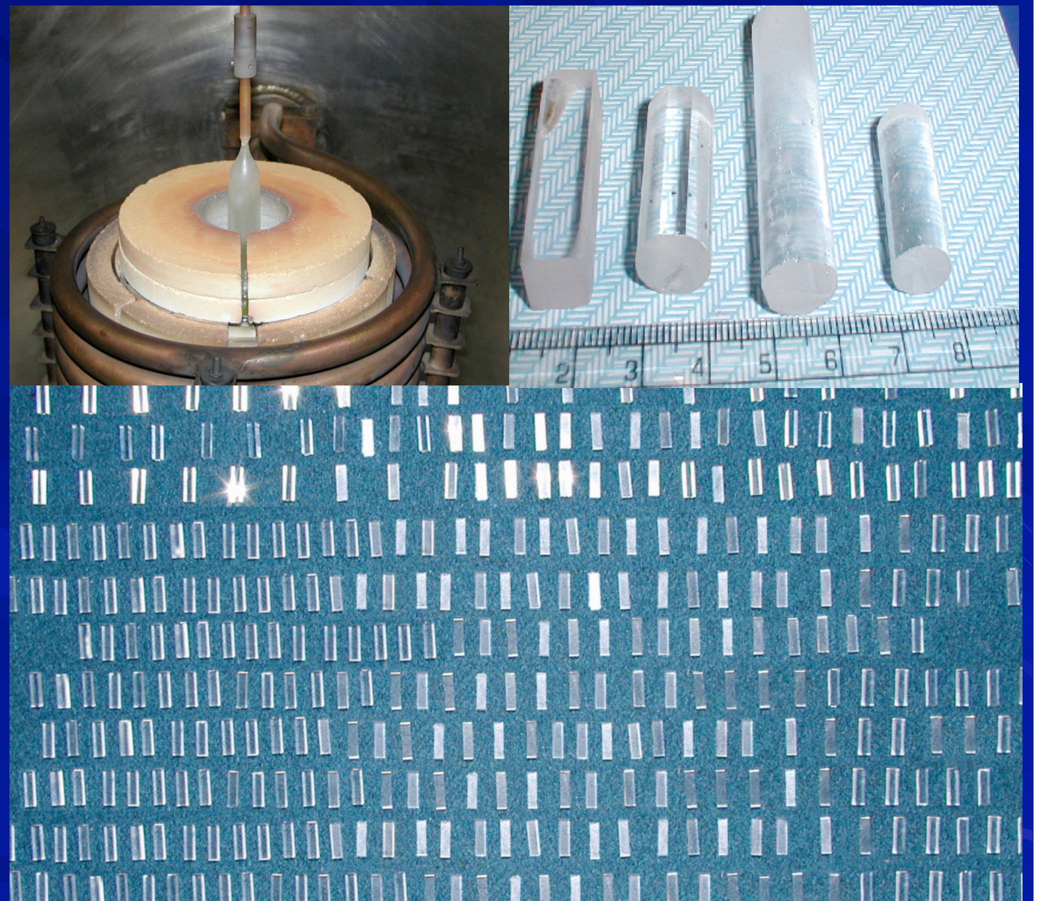
R & D examples

1- Crystals

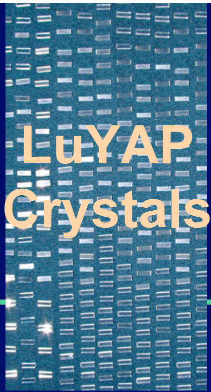
CMS $PbWO_4$ production



Crystal Clear LuAP production



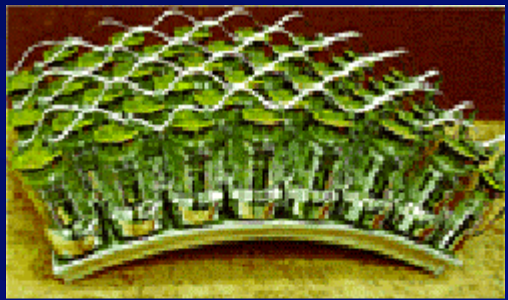
Scintillators for PET



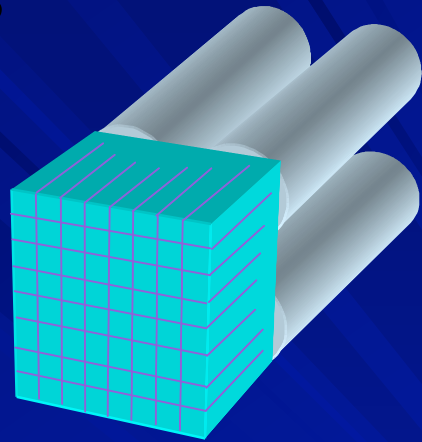
	1962	1977	1995	1999	2001	
	NaI	BGO	GSO:Ce	LSO:Ce	LuAP:Ce	LaBr3
Density (g/cm^3)	3.67	7.13	6.71	7.40	8.34	
Atomic number	51	75	59	66	65	
Photofraction	0.17	0.35	0.25	0.32	0.30	
Decay time (ns)	230	300	30-60	35-45	17	
Light output (hν/MeV)	43000	8200	12500	27000	11400	
Peak emission (nm)	415	480	430	420	365	
Refraction index	1.85	2.15	1.85	1.82	1.97	
Hygroscopic	Yes	No	No	No	No	
Natural radioactivity	No	No	Yes	Yes	Yes	

No Scintillator with Superior Properties in *All* Aspects

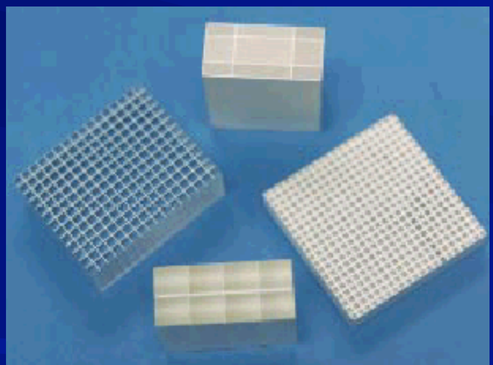
Detectors → crystals



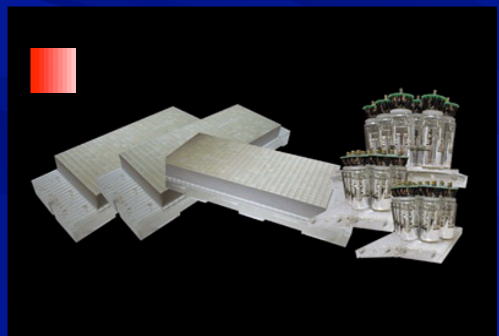
NaI curved
CPET (Philips)



Detection block
Crystals 4x4x20 (or 30) mm^3
Block 8 x 8 crystals , 2 x 2 PM's



GEMS
BGO (Bicron)

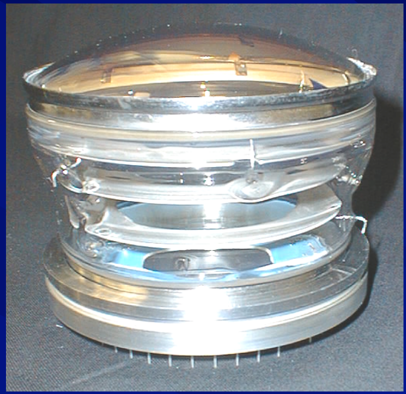


ADAC Philips
GSO

CTI Siemens
LSO

2- New pixellised Photodetectors

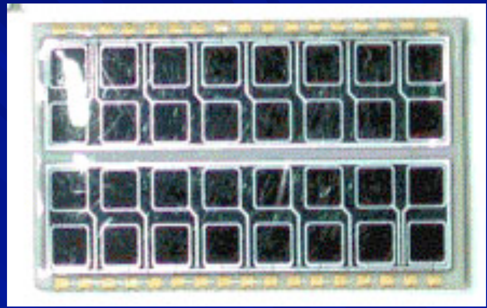
LHCB



BrainPET

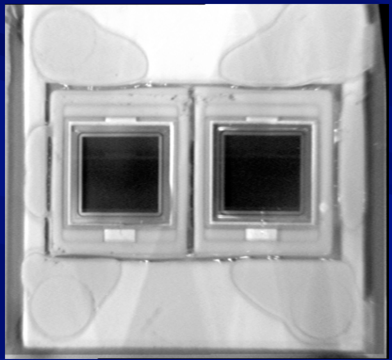
HPD tube
manufactured at
CERN: 2048 channels

ClearPEM



Hamamatsu 32
channels APD array

CMS



Hamamatsu single
channel APD

Opera

Hamamatsu H7546
64 channel PMT

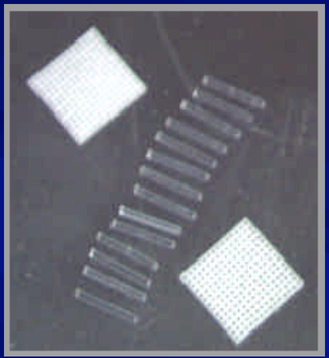
ClearPET

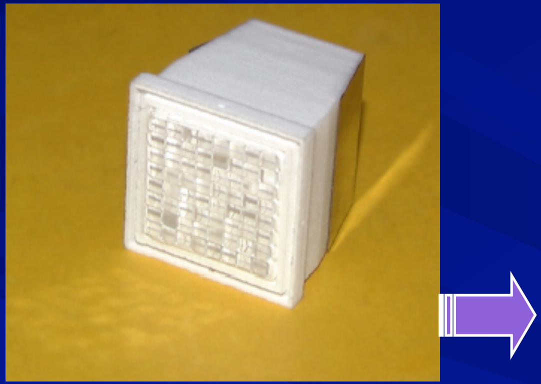
Mammography

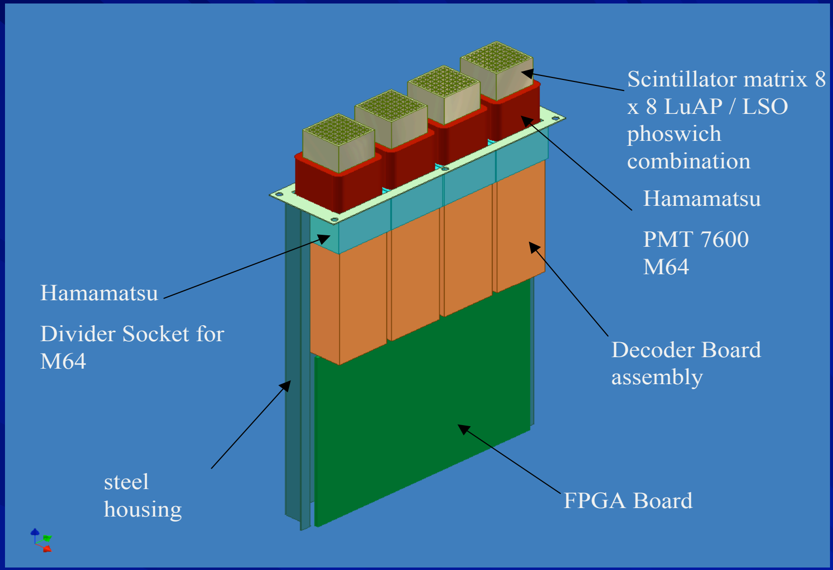
Hammamatsu
PM flat pannel

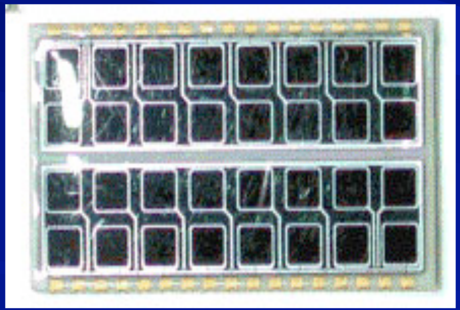
State of the art technologies

A Small Animal PET device
Licensed to industry (ClearPET)

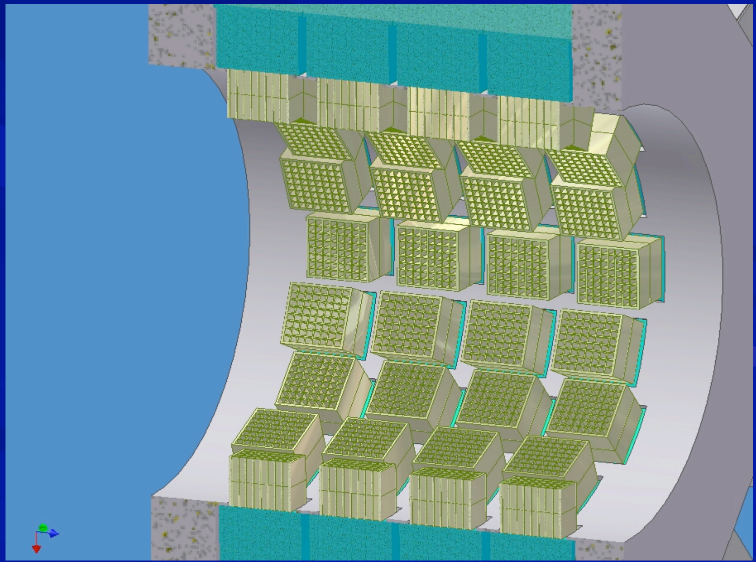






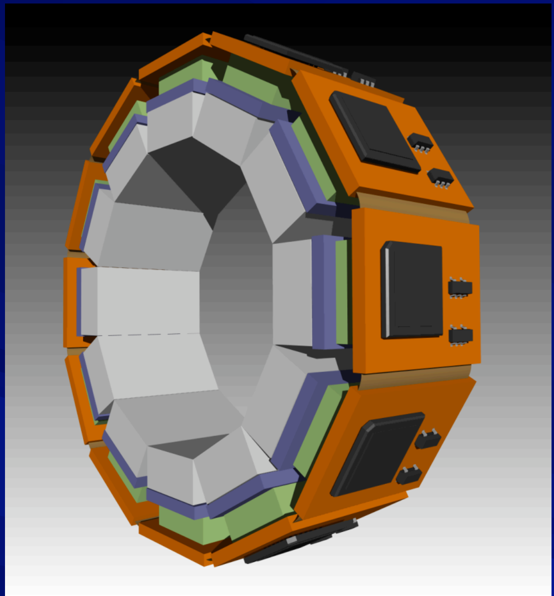


Hamamatsu 32 channels APD array



(courtesy of P.Lecoq/CERN)

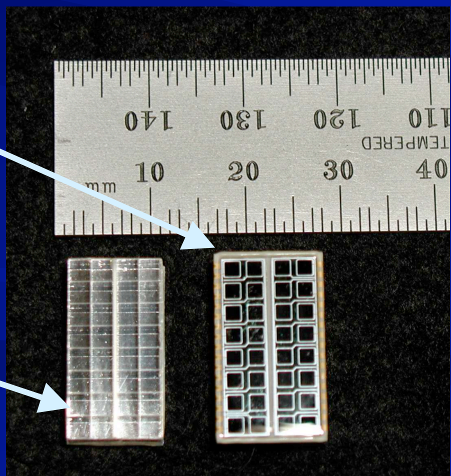
The Rat Conscious Animal PET scanner,
J.F. Pratte, et al., BNL

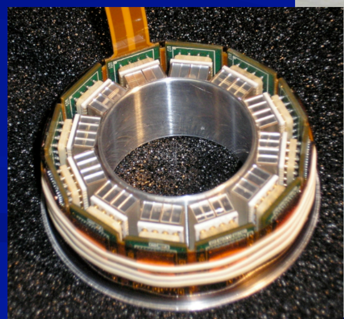


Ring containing 12 block detectors
Up to two layers of 2x2 x5 mm deep LSO crystals with APDs and integrated readout electronics

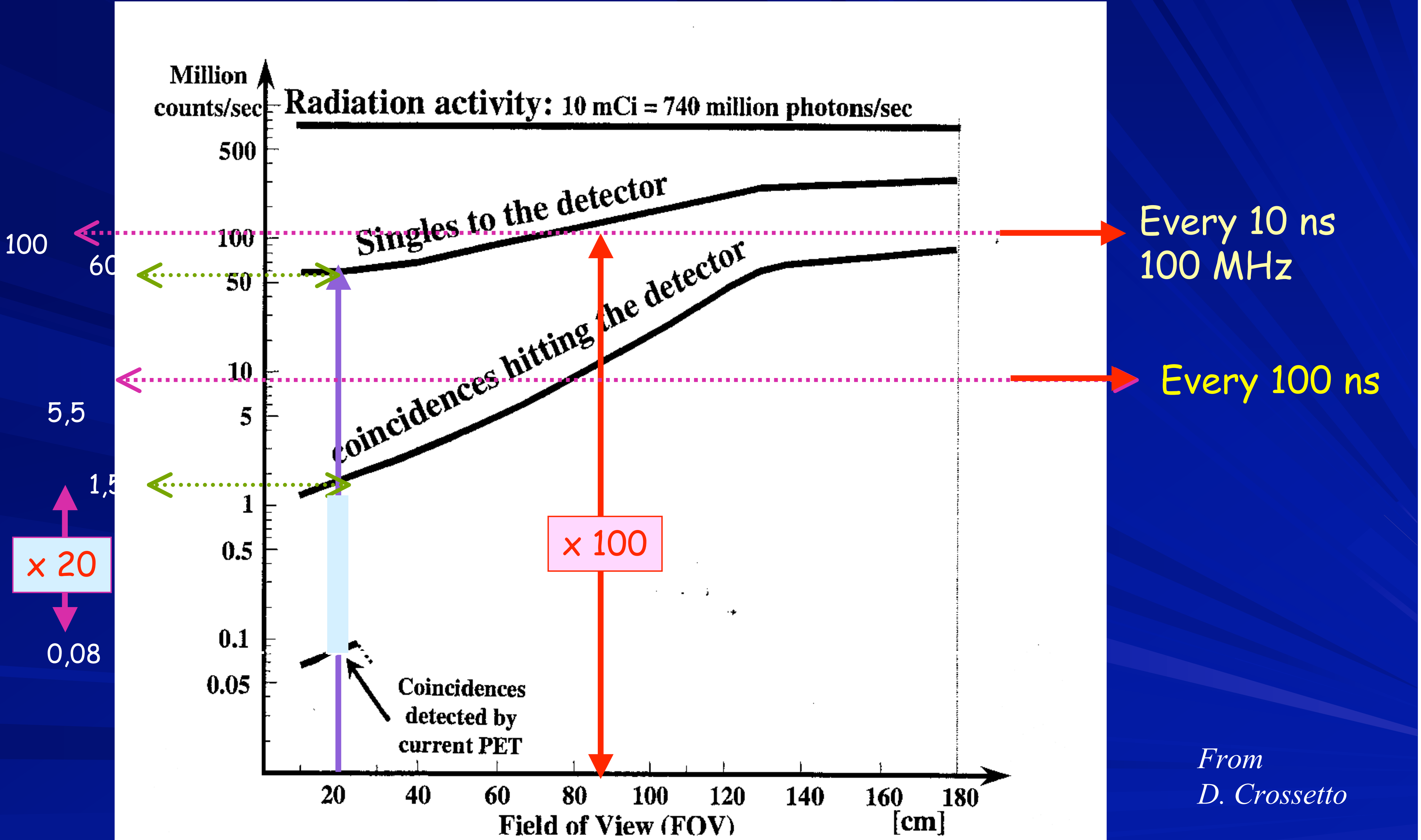
APD (Hamamastu S8550)

LSO array





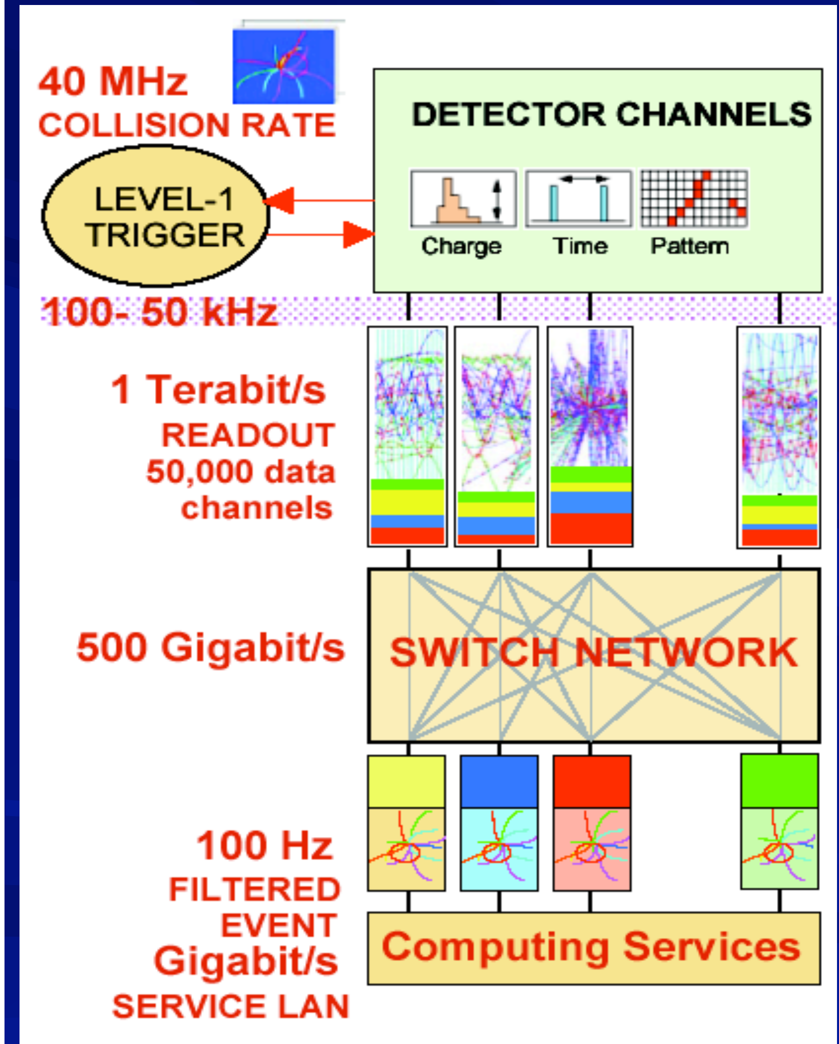
Counting rate estimate



From D. Crossetto

4- Pipeline Architectures

LHC

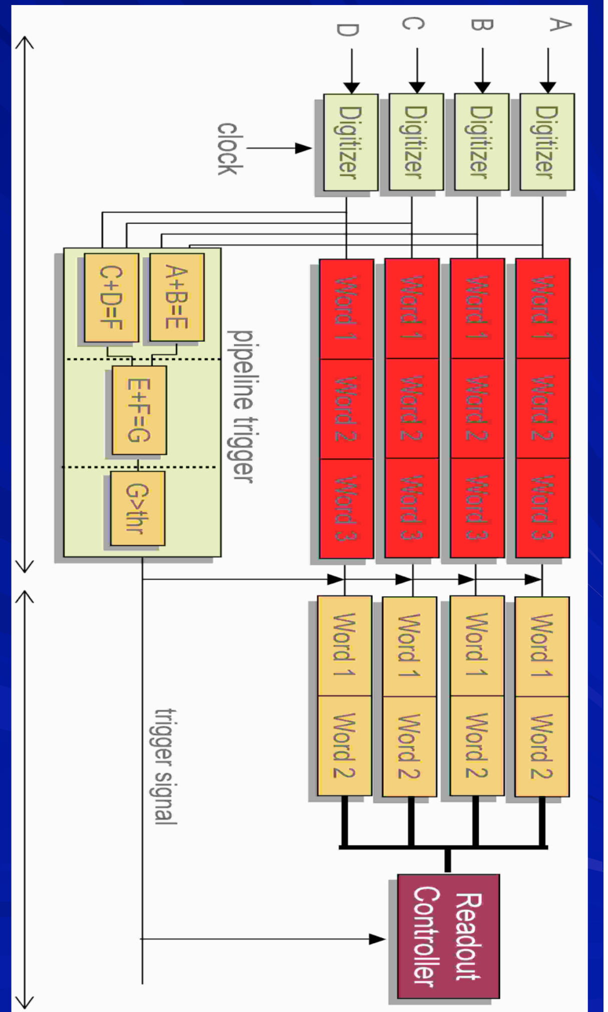


Digitisation

Pipeline

Event builder

Future PET



Dead Time

Time during which the detector can not accept and record new events

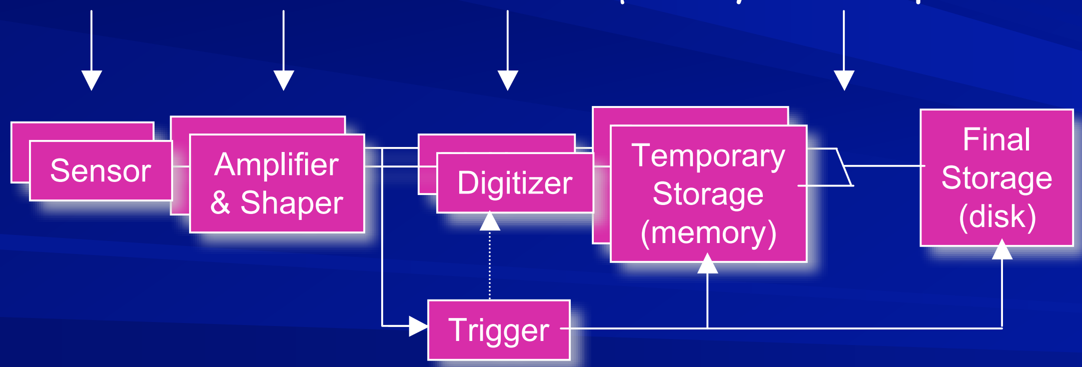
R = Rate (s^{-1})
δ = Absolute dead time per event (s)
DT = Relative dead time (%)
AR = Acquisition rate (s^{-1})

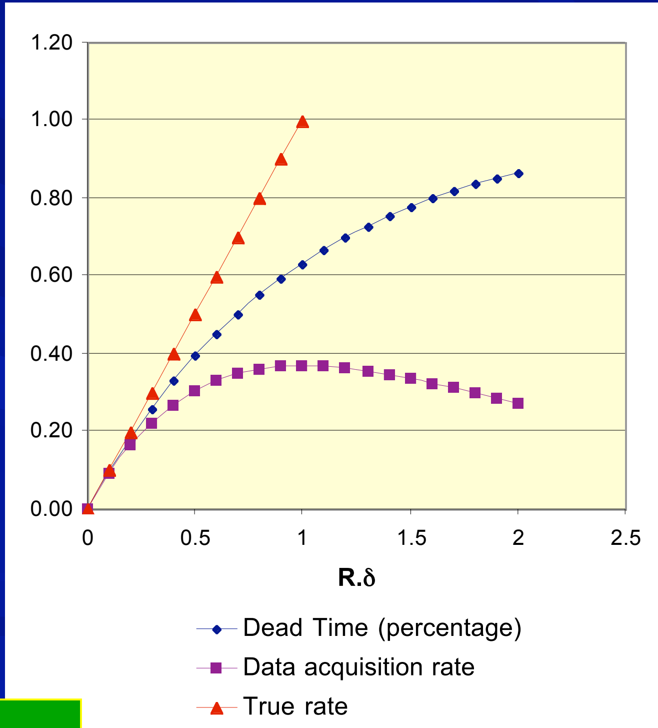
$$DT = 1 - e^{-R\delta}$$

$$AR = R \cdot e^{-R\delta}$$

Dead time sources:

Detector signal formation	Signal shaping	Conversion time	Readout time
20-100 ns	100-500 ns	10 ns-100 μs	System dependent

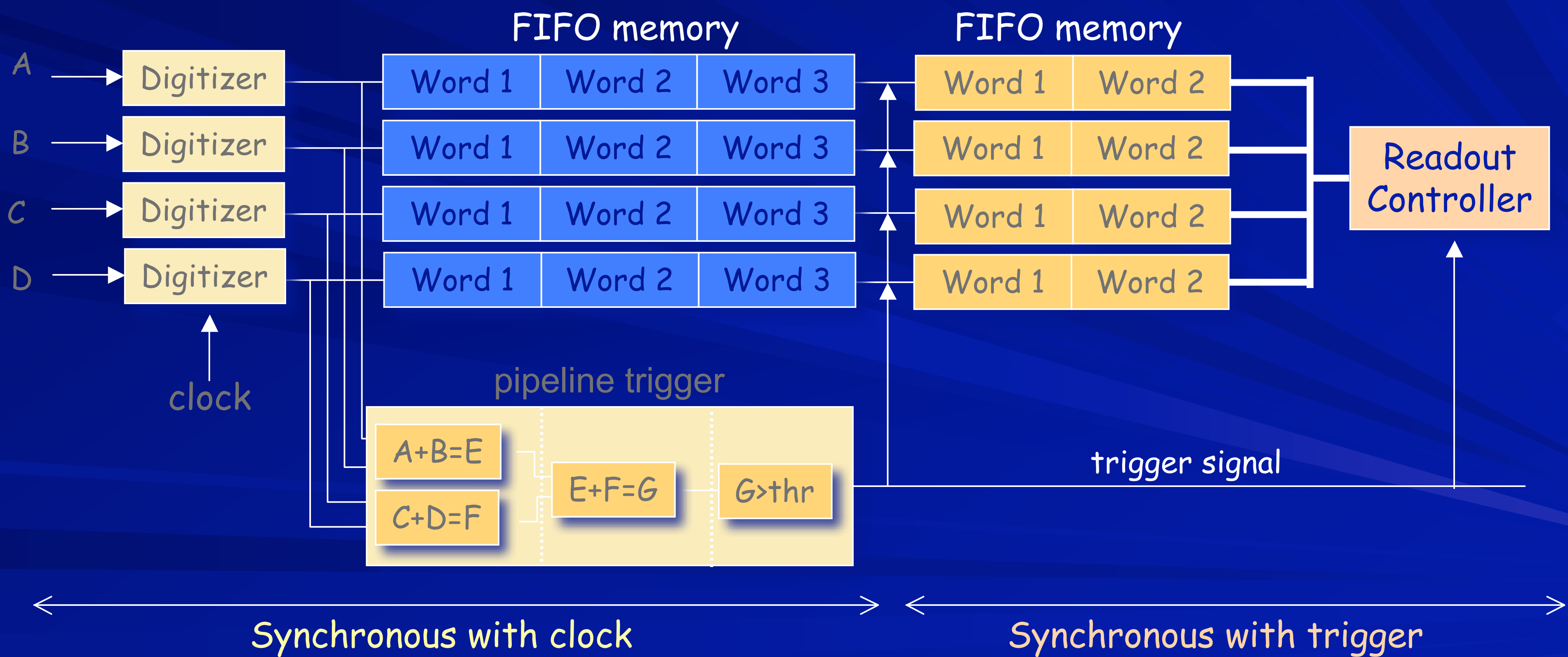




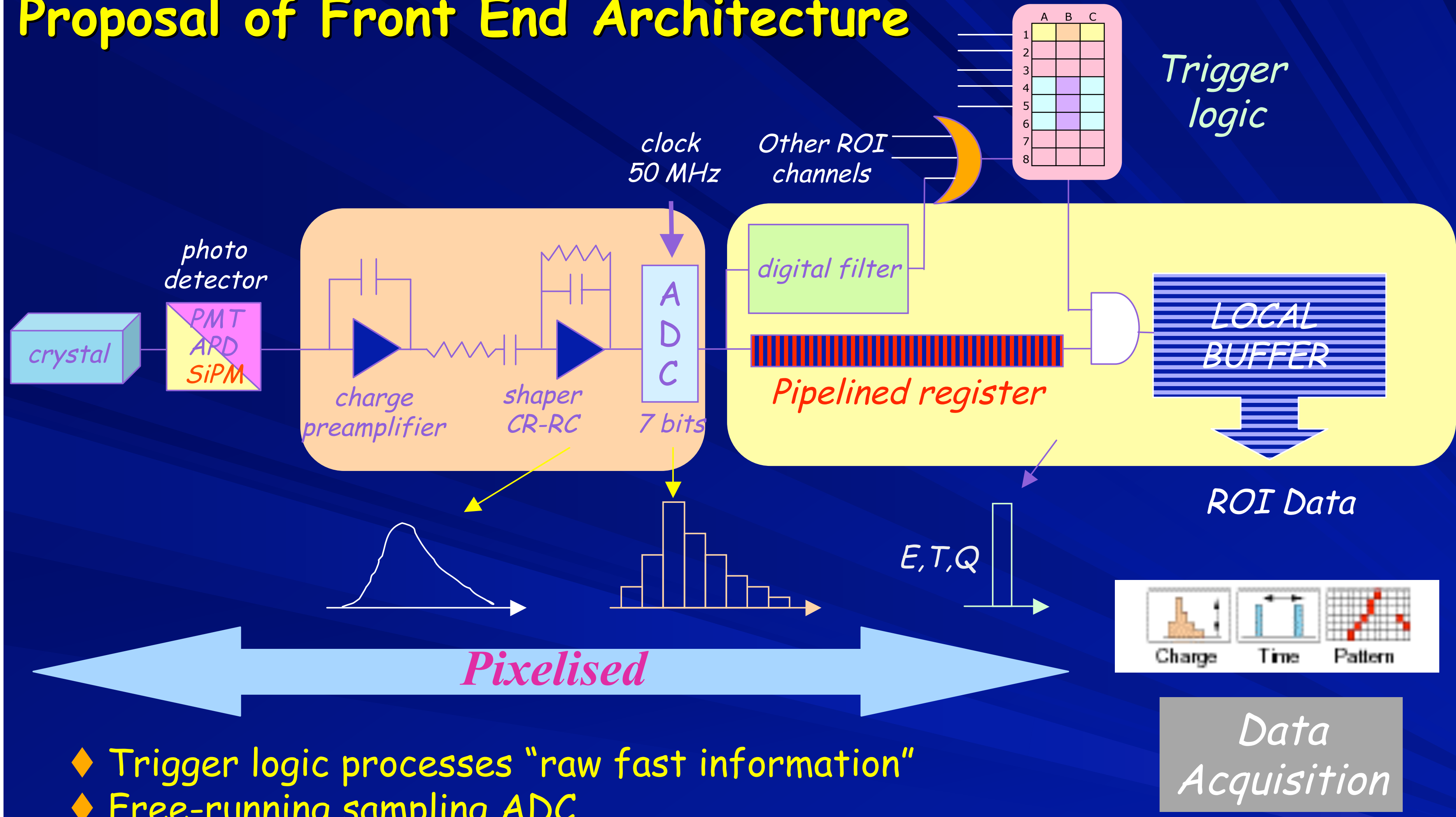
Pipeline Architectures

- Architectures based on multi-event storage and pipeline trigger processing
- Allow to minimize the data acquisition dead time

Example with 4 channels and trigger A+B+C+D>threshold



Proposal of Front End Architecture



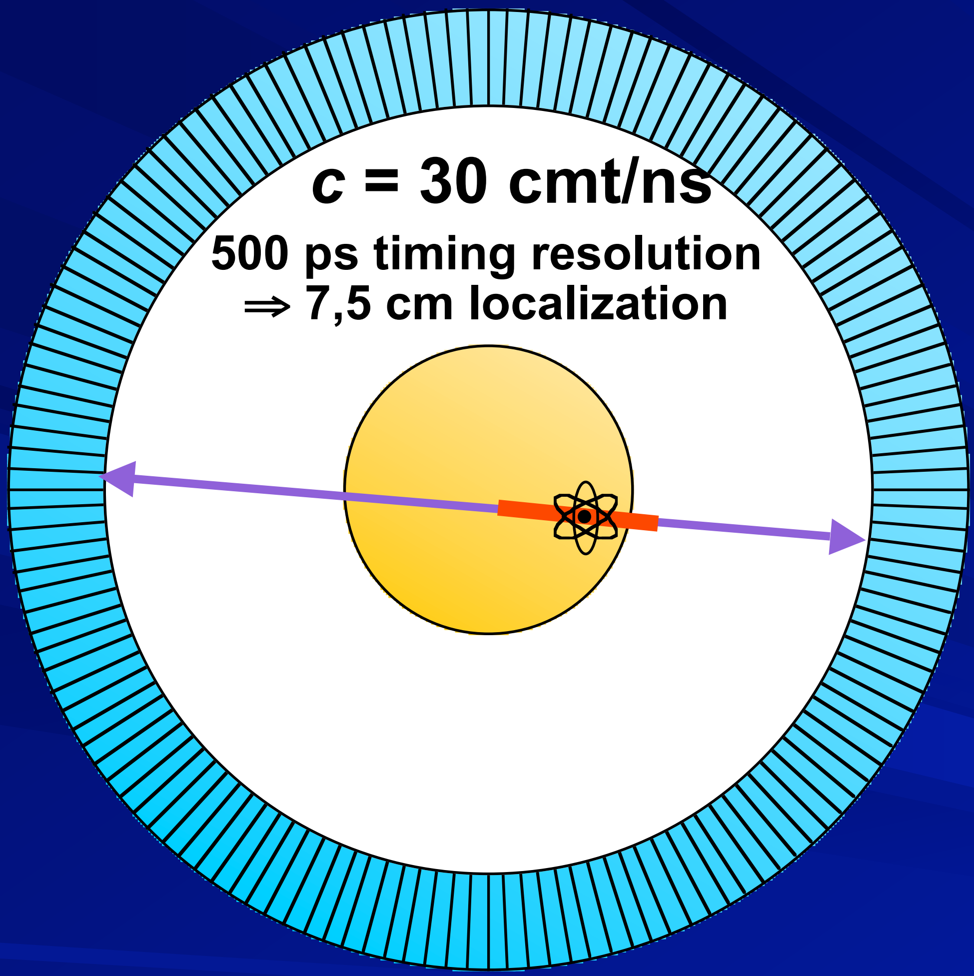
- Trigger logic processes "raw fast information"
- Free-running sampling ADC
- Digital filter used to extract pulse amplitude and high resolution timing
- Pipelined processing architecture to avoid deadtimes
- Only one "channel" to compute either the energy and time

Towards an innovative read out electronics concept (INNOTEP)

♦ Truly pixelising the detector yields to a considerable number of channels to be considered, each having its own reading electronics
♦ size and speed have been a real issue for years but progress in the microelectronics field have made ASICs of high integration readily available
♦ besides this, they appear as a cost effective solution
♦ no possible CFD implementation on chip (shared constant network / derivation are noisy…!) in agreement with the expected time resolution.
♦ High resolution TDCs require complex architecture, large surface area and appearno

→ need to find another solution for time measurement … to be inspired by HEP experiments

Next → Time-of-Flight in PET ?

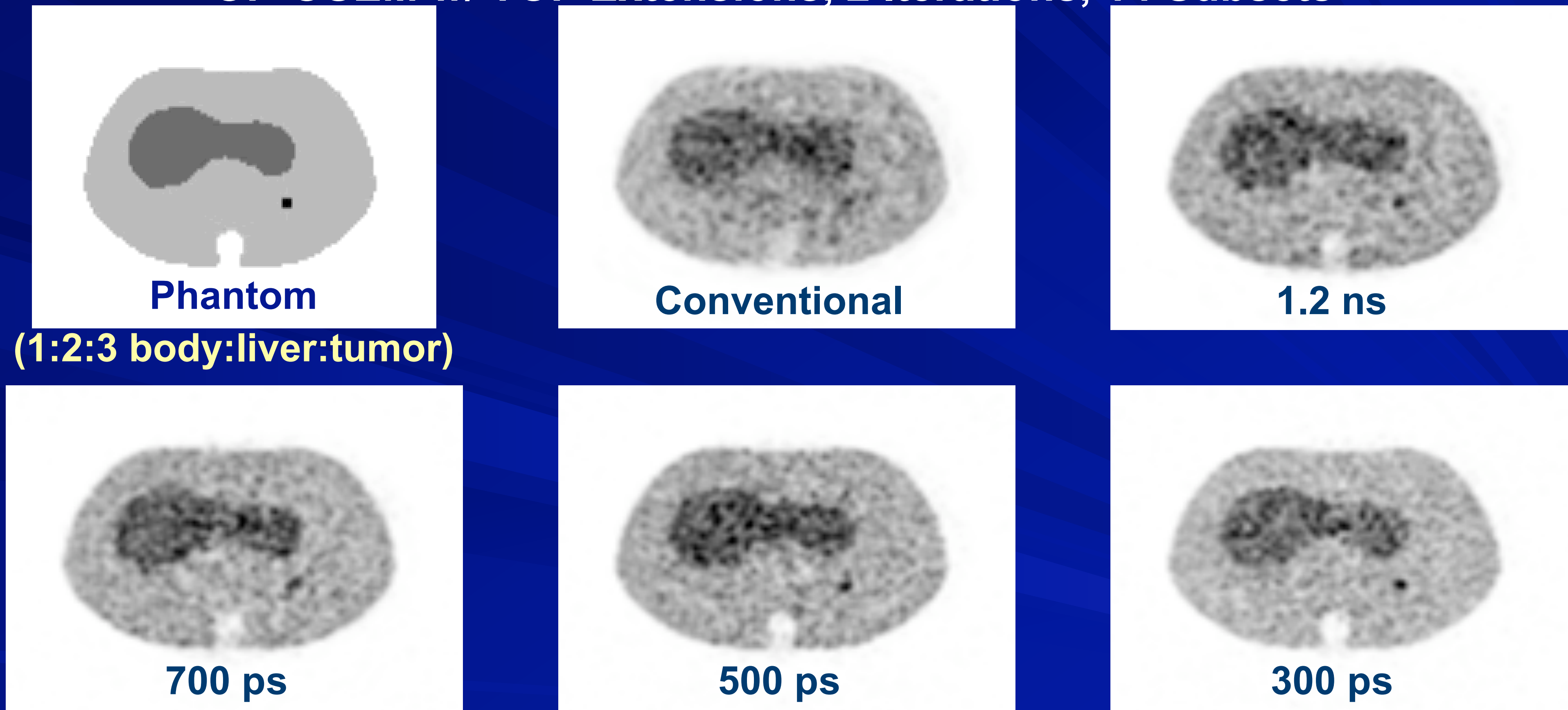


- Can localize source along line of flight.
- Time of flight information reduces noise in images.
- Time of flight cameras built in the 80's with BaF2 & CsF.
- These scintillators forced compromises that prevented TOF from flourishing
- Today new crystals (LaBR3) and new MHz electronics/DAQ

- Objective : < 500 ps Timing Resolution

Whole-Body TOF Simulations

$2\text{x}10^6$ Trues, $1\text{x}10^6$ Randoms, Attenuation Included
OP-OSEM w/ TOF Extensions, 2 Iterations, 14 Subsets



Clear Improvement Visually

*Data courtesy of Mike Casey, CPS Innovations

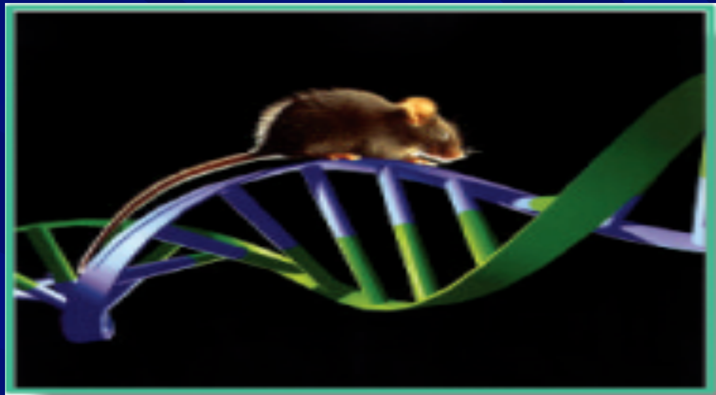
The future of medical imaging

- Faster exams
- Movement correction
  - Breathing
  - Cardiac beating
  - Digestive bolus
- Dynamics
- Quantification
- True multimodality
- Reduce dose to patient

IMPROVE

- Spatial resolution
- Timing resolution
- Sensitivity
- Signal/Noise ratio

Molecular Imaging in Medicine & Biology



- At present
  - Tissue sample during surgery or after biopsy
  - Molecular analysis to define the tumor characteristics
    → molecular signature

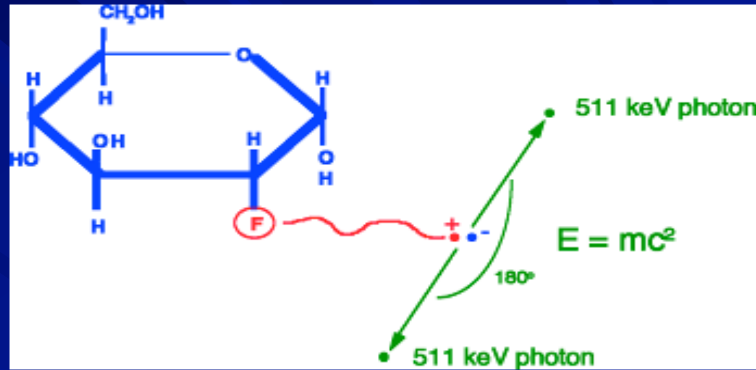
- In the near future
  - Tissue sample by imaging before surgery
  → molecular signature

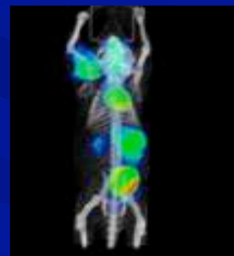
PET Molecular Imaging

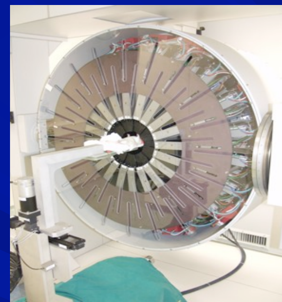
Accelerator

- ^{15}O
- ^{13}N
- ^{11}C
- ^{18}F

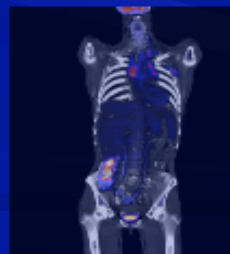
2-[F-18]Fluoro-2-Deoxy-D-Glucose (FDG)







Pre-Clinical



Clinical

Future Challenges

Whole-Body High-Resolution ‘Minute’ PET

- Very large number of channels (20 → 80 cm FOV)
  ~ 300 k channels (2x2 mm2 pixels)
- High trigger rate ~ 10 MHz
  (10 mCi, 20% sensitivity)
- High data rate
  ~ 10 Gbyte/s (1 kbyte event size)
- Large number of events
  ~ 10^9 events (10^6 voxels, 1000 events/voxel)
- Large data volume per image
  ~ 1000 Gbytes (list mode)
- High computer power for image reconstruction

Improve spatial resolution ?

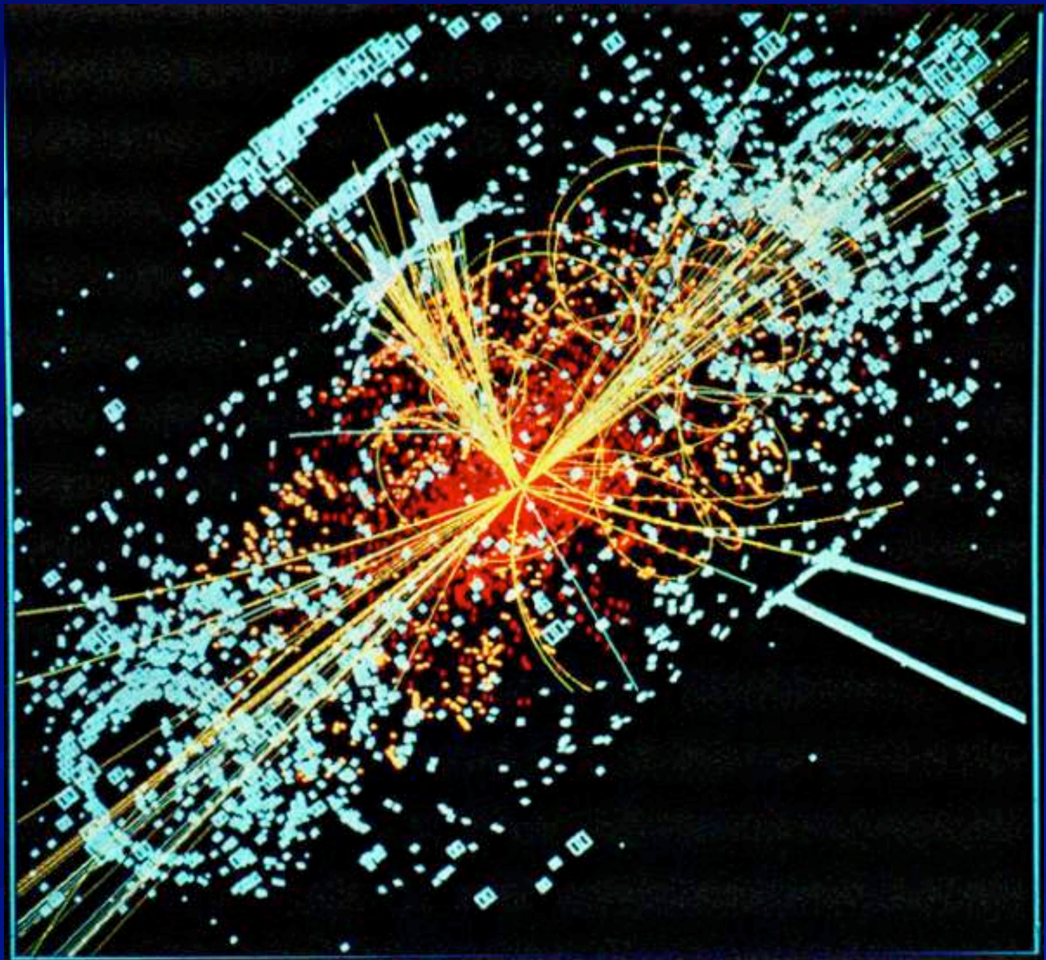
- Near theoretical limit = few mm (4mm with FDG)
- Can Increase SNR by Reducing Backgrounds
- Keep exam time short (30 min → few min!)

Sensitivity → significant room for improvment!

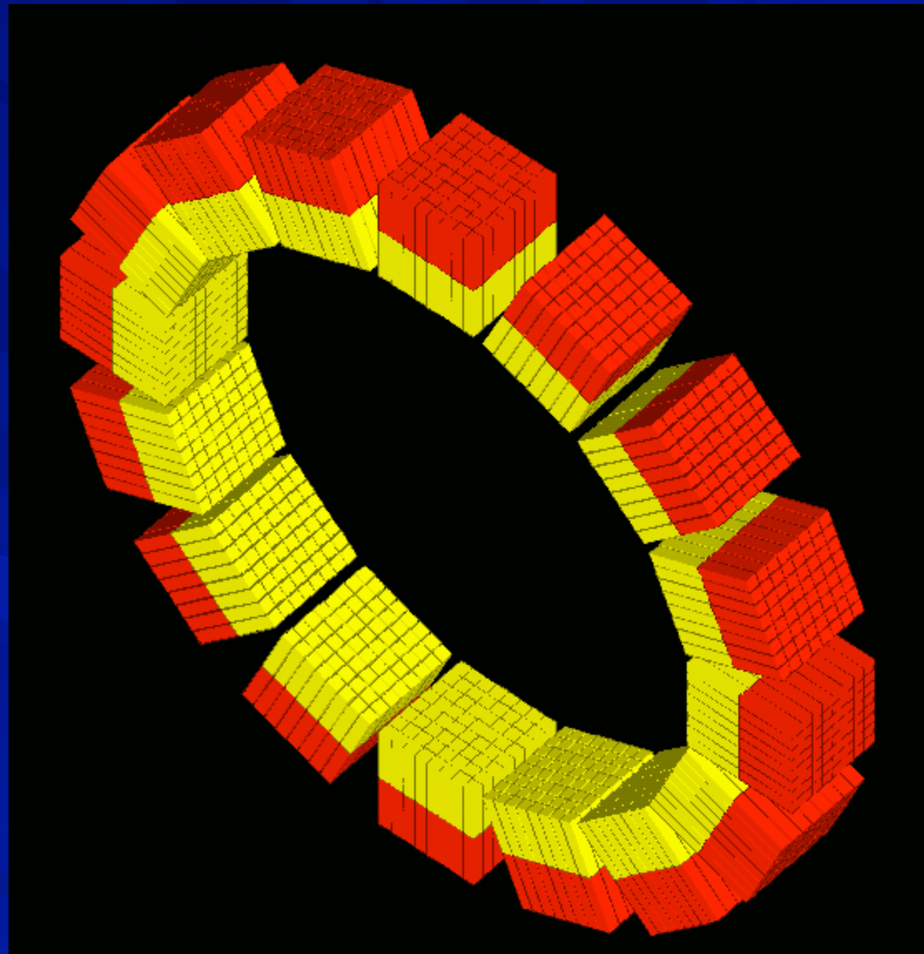
- Compact and hermetic design → large Field Of View
- Fast and high light yield crystal (LaBr3)
- Fast and low noise electronicswith TOF capability
- Built-in intelligence in the Data Acquisition system
- Make the best use of "good" events (TRIGGER)
- Use Compton events instead of rejecting them?
- Efficiently throw away "bad" events (better timing resolution!)

5- Simulation

Higgs event at LHC (CMS) with Geant4



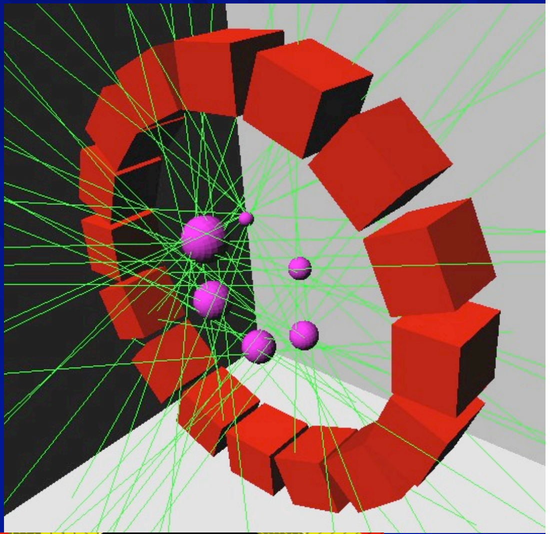
ClearPET with GATE: Geant4 Application for Tomographic Emission

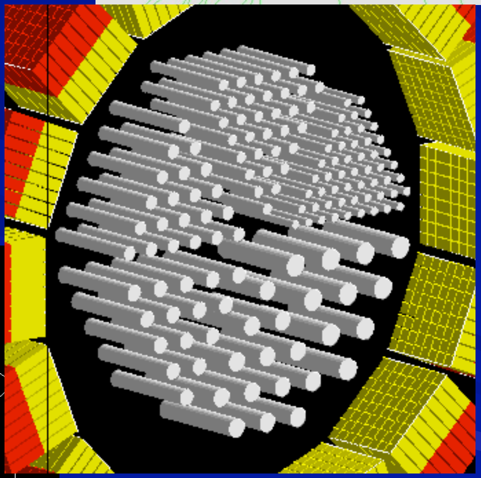


GATE : Geant4 Application for Tomographic Emission

Monte-Carlo simulation allowing to :

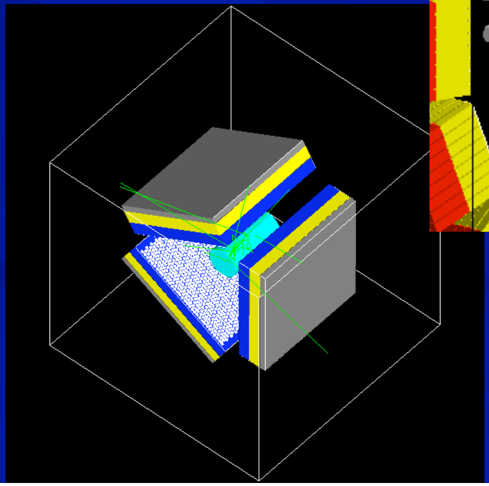
✓define geometries
(size, materials,…)
✓ define sources
(geometry, nature, activity)
✓ choice of physical process
(low energy package of G4)
✓ follow track point by point



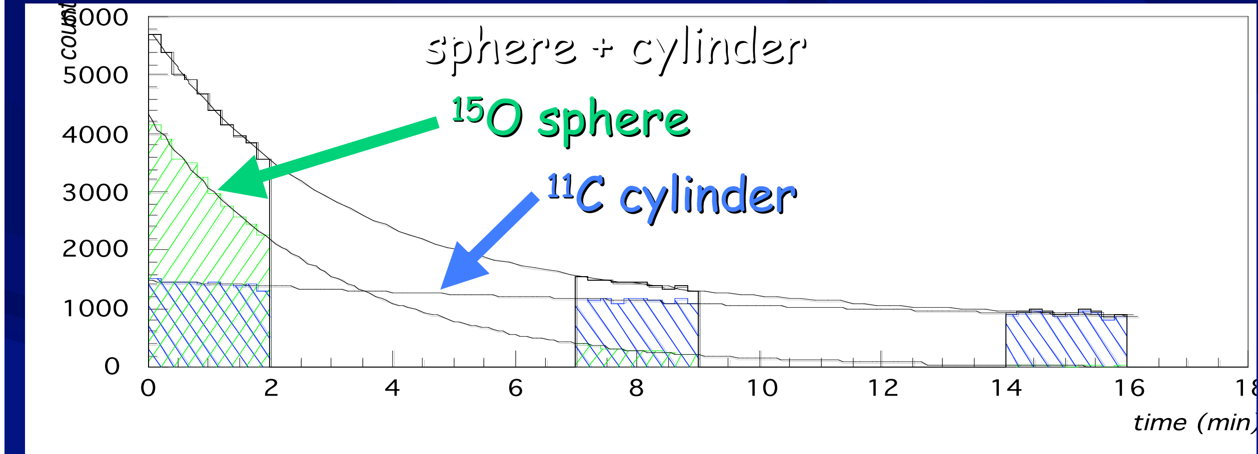


GATE specificities:

✓CERN GEANT4 libraries
✓Time modellign
(sources , movement,random…)
✓Script language(avoid C++)
✓Code interactivity
✓Sharing development

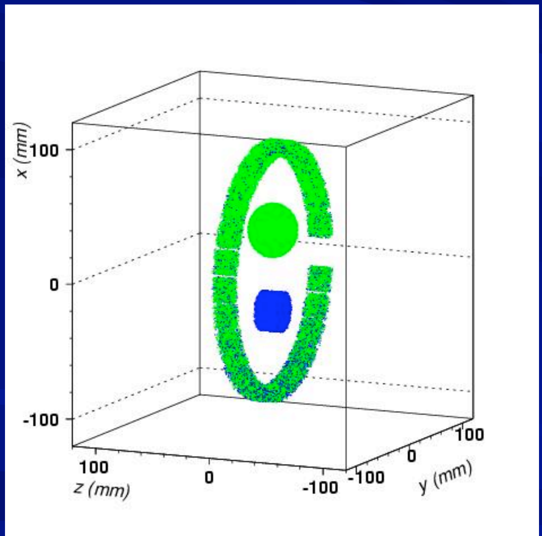


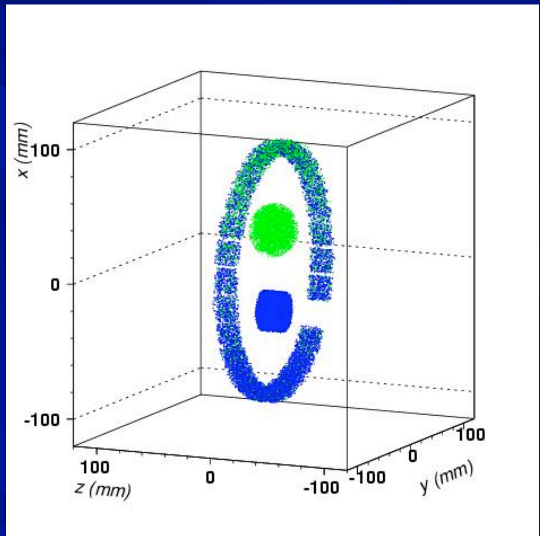
Simulation of decaying sources

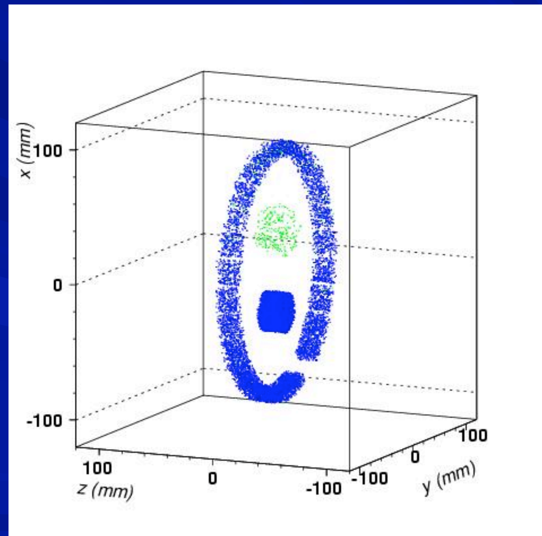


^{15}O (2 min)

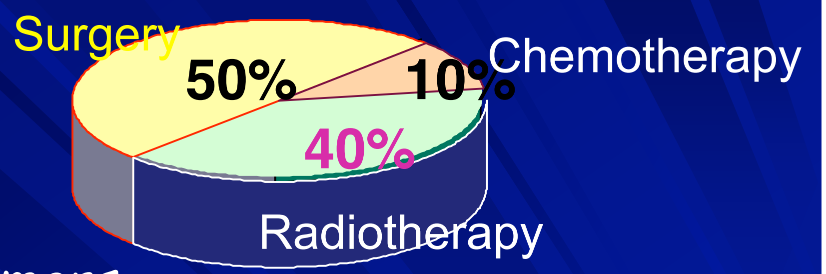
^{11}C (20 min)







Radiotherapy :Context



- **Radiotherapy:**
  - Use ionizing radiation to treat and cure tumors
  - Frequent treatment (2/3 of cases) → 160 000 /year in France.
  - Efficient treatment → 30 to 40% of recovery
  - → **Failures due to radioresistant tumors!**
  - Allow good quality of life → tolerance
    - non invasive, itinerant and without important physical effects.
  - Cheap → 5% of the cancer budget (500 M€)
  - Essentially X (Linear accelerators) & photons (curietherapy)

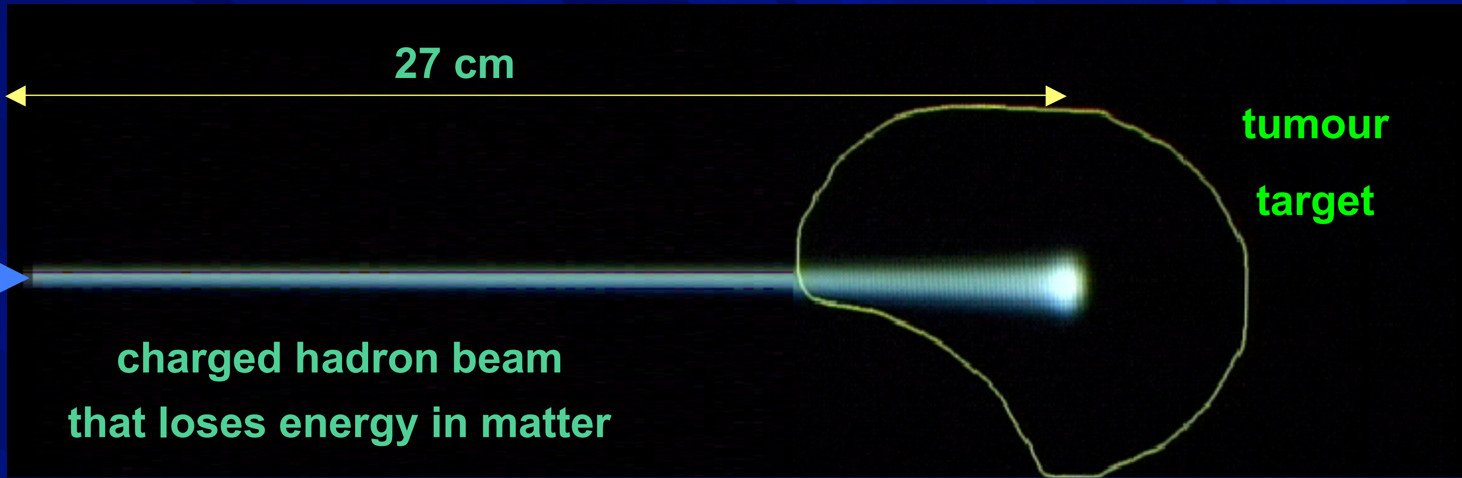
- Why Radiotherapy X is NOT 100 % efficient?
  - Local irradiation → 100 Gy = 90 % of sterilization
  - Complication < 5 %
  - Tolerance of saine tissue is the limiting factor of Rx
  - Technological progress = improve ratio: **tumor dose / sain tissue dose**

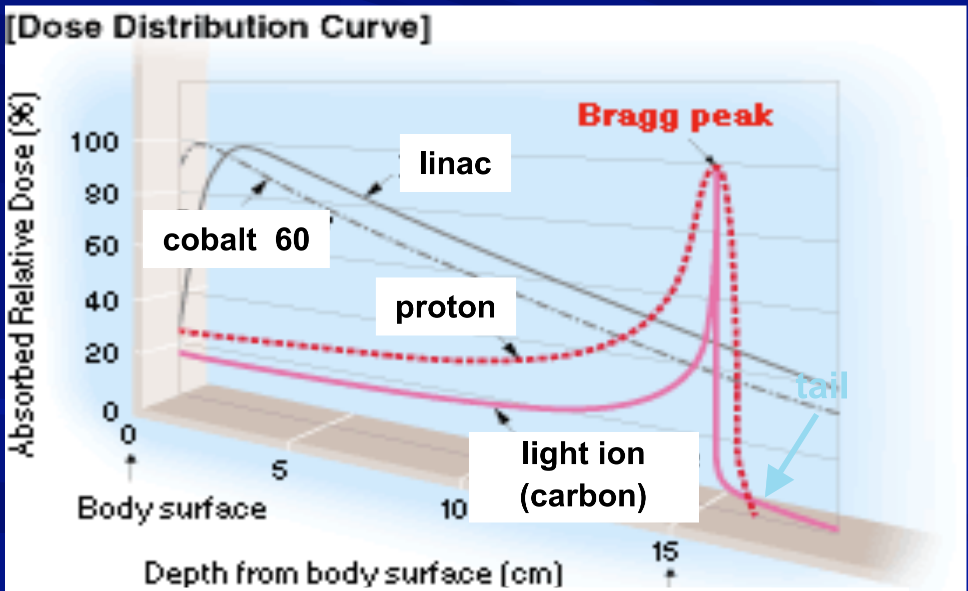
Hadrontherapy accelerators the rationale

200 MeV - 1 nA protons

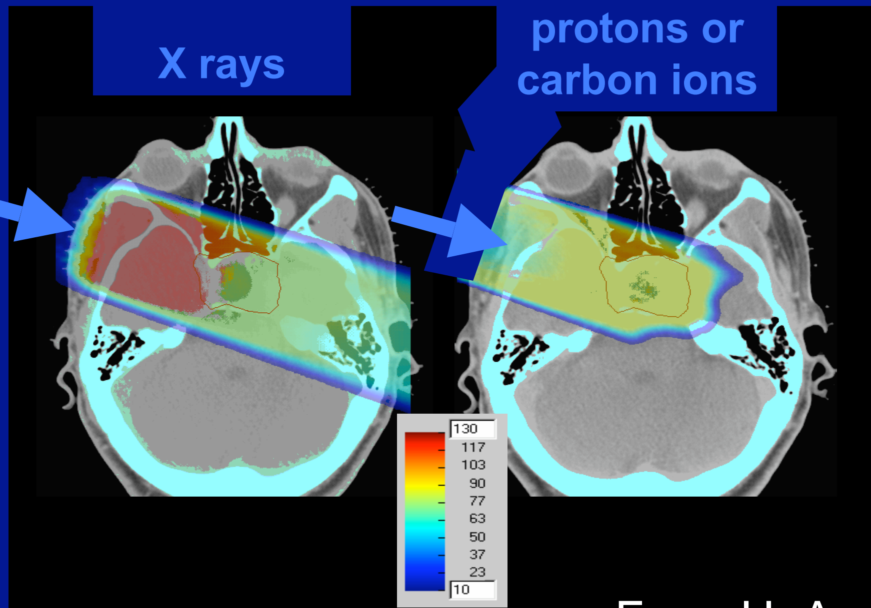
4800 MeV – 0.1 nA carbon ions

which can control radioresistant tumours



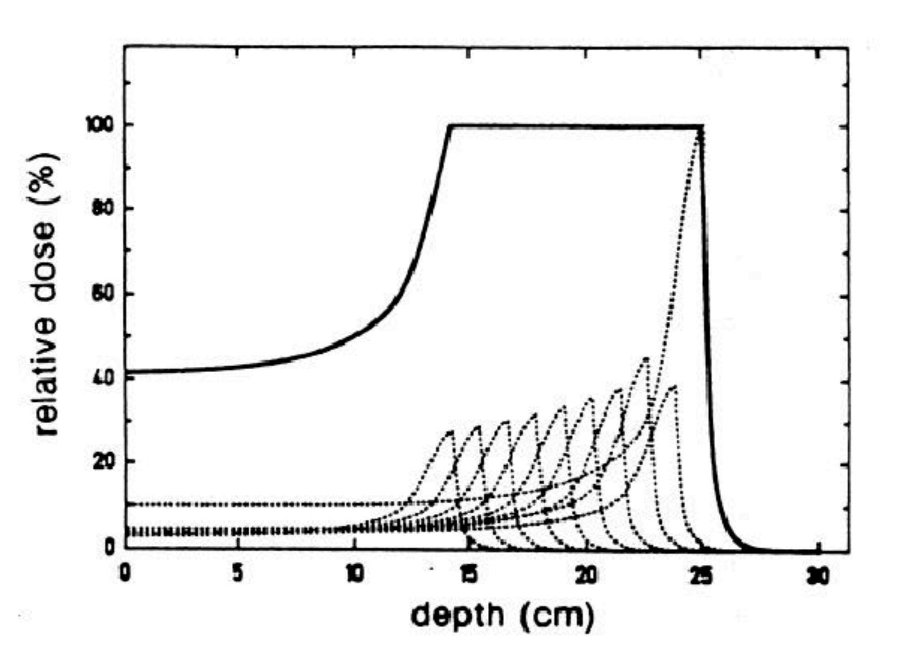


http://global.mitsubishielectric.com/bu/particlebeam/index_b.html

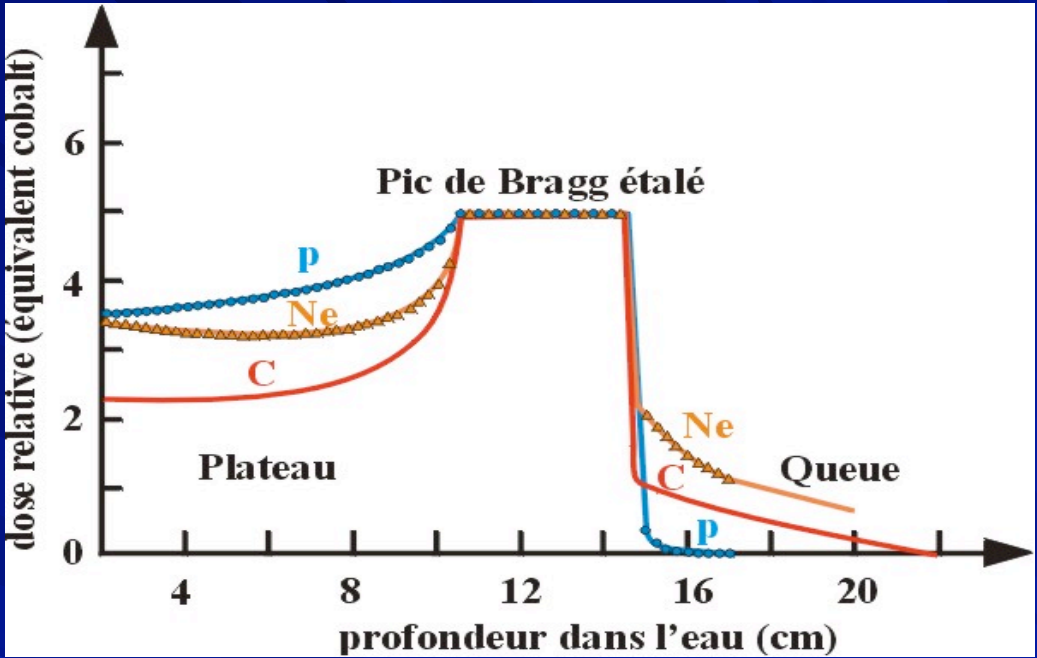


From U. Amaldi

How to irradiate the tumor ?

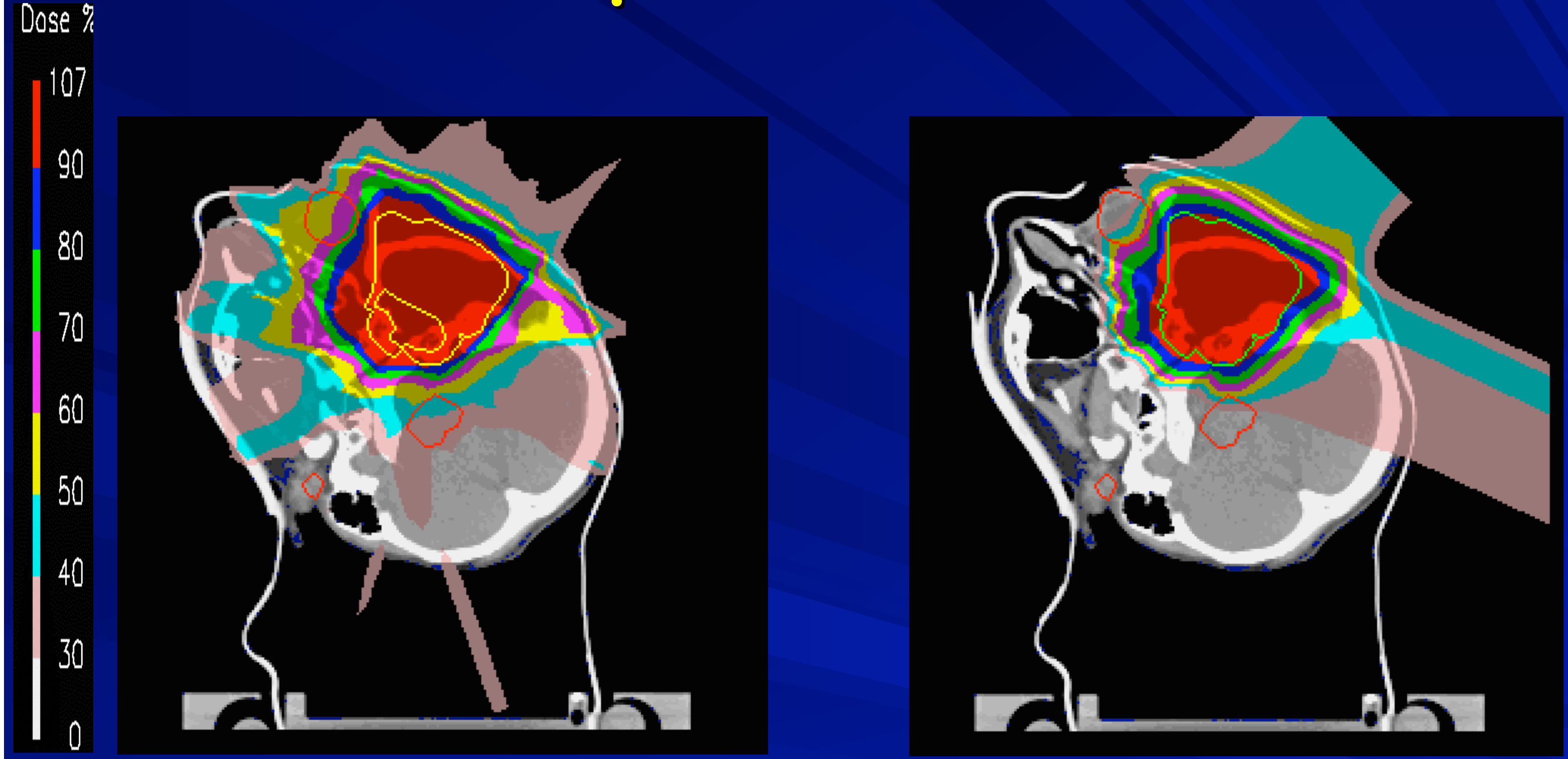


Spread Bragg peak



- **Treatment in depth → combine**
  - Energy modulation → Scan the energy to make a Spread Out Bragg Peak (SOBP) that spans the tumor
  - Intensity modulation

Comparison with Photons

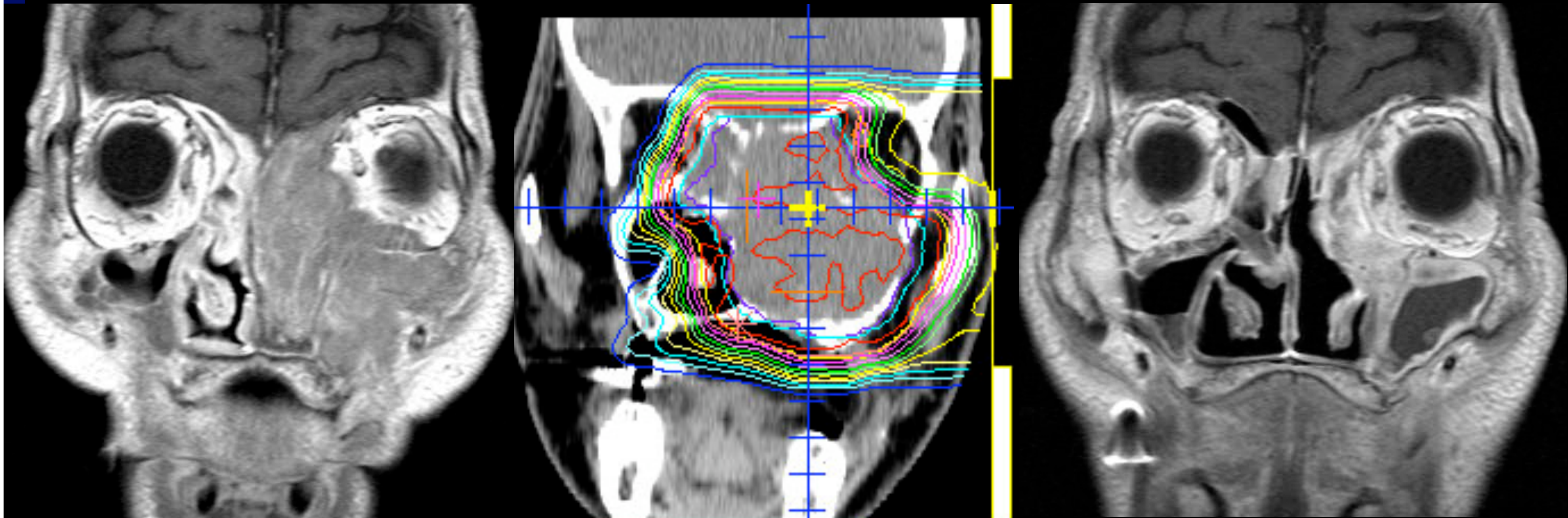


state-of-the-art photon therapy (IMRT)

Proton therapy (spot scanning)

Carbon Ion Radiotherapy

73M Lt. Nasal Cavity Malignant Melanoma T4N0M0 57.6GyE/16fr/4w



Before **2 months after RT**

Specific Aims of PET in Heavy Ion Therapy

- Verification of treatment plan *in vivo* prior to dose delivery
  - ≈ measure the beam stopping point with high <u>spatial</u> accuracy (<1 mm)

    → *High spatial resolution*
    → *High sensitivity*

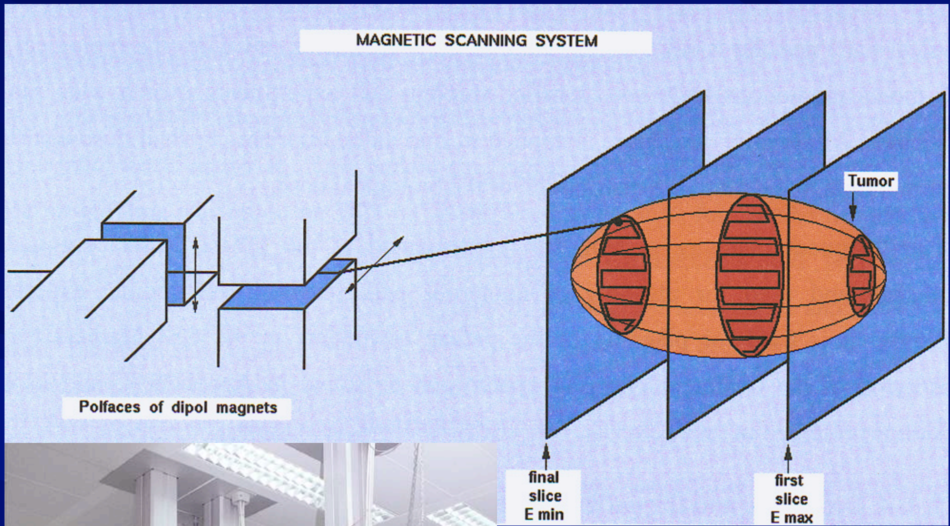
- Monitor dose distribution "in-beam"
  - ≈ measure b⁺ activity with high <u>quantitative</u> accuracy

  → *High sensitivity (→ high SNR !)*
  → *High count rate capability*
  → *Fast image reconstruction (real time..?)*

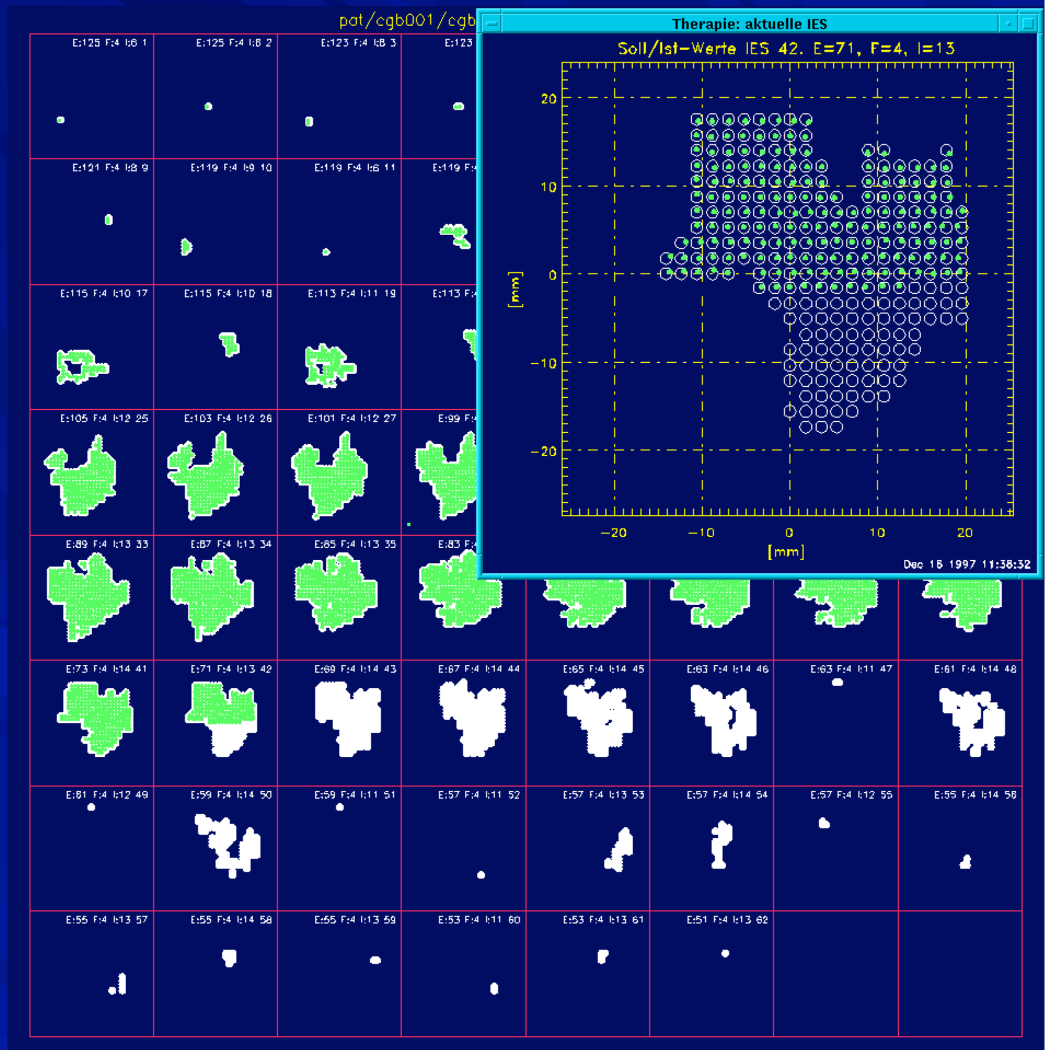
R & D → Some areas of interest

- Beam production
  - New synchrotrons!
  - Active scanning of the tumor
- Beam monitoring and dosimetry →
  - Solid state and micropattern detectors,fast electronics …
- Patient dosimetry
  - In beam PET → On line monitoring of deposited doses need high resolution and high sensitive PET in real time environment
- Proton CT →
  - Particle telescope (solid state or gazeous) and calorimeters, fast electronics

GSI treatment planning using « active » scanning

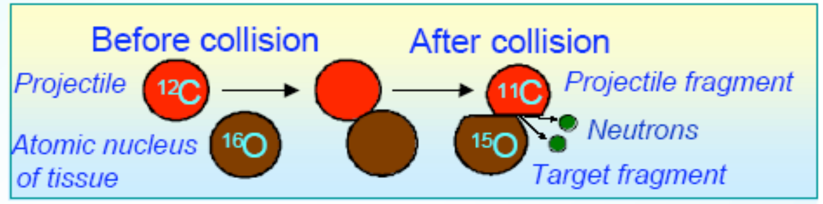


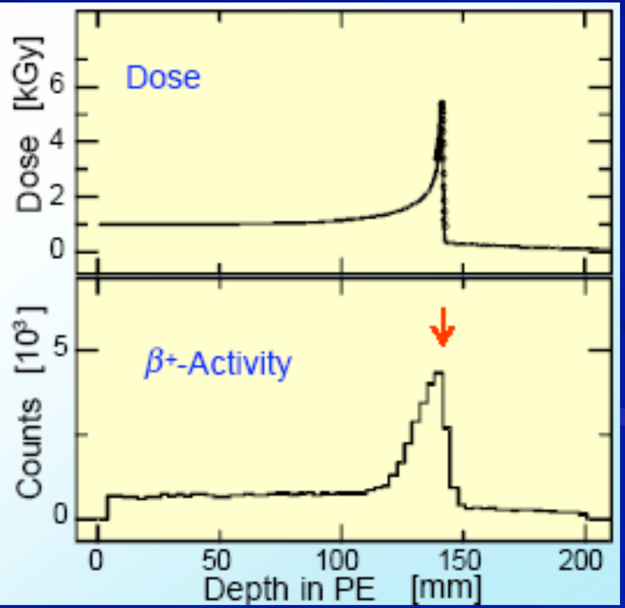
Treatment room at GSI



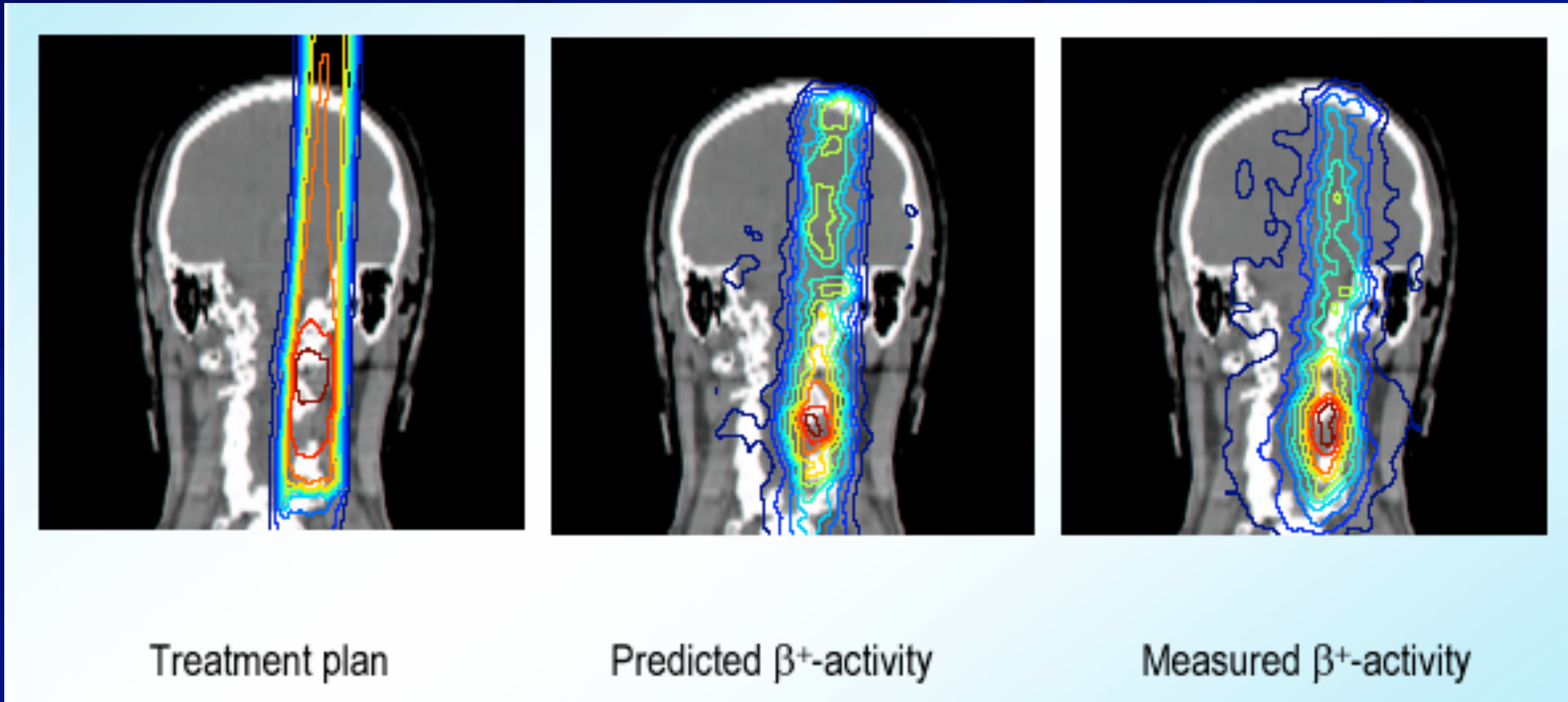
In Situ PET Control of light Ion therapy physical basis

- Activation of the irradiated tissue by positron emitters (11C,10C,15O…)
  - By product of the therapeutic irradiations
- Detection by PET
  - In beam, in situ, non invasive
- Relation between dose and β^+ activities
  - Beam position, particle range
- Cross sections
  - 12C + O16 → 15O : 84 mb
  - 12C +12C → 11C : 56 mb
  - 12C + 12C → 5 mb





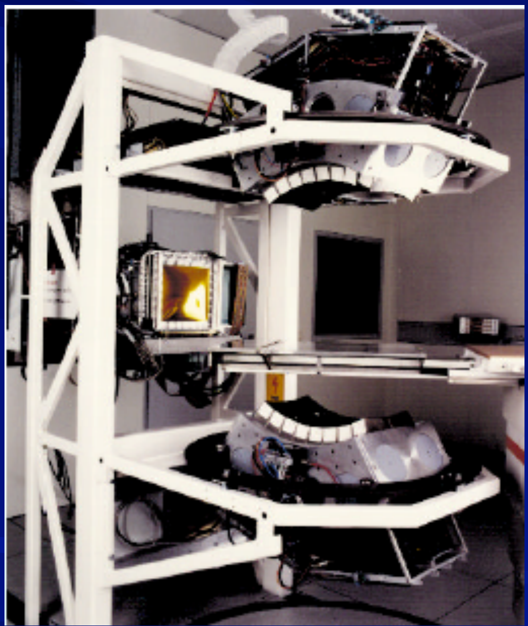
Clinical results at GSI

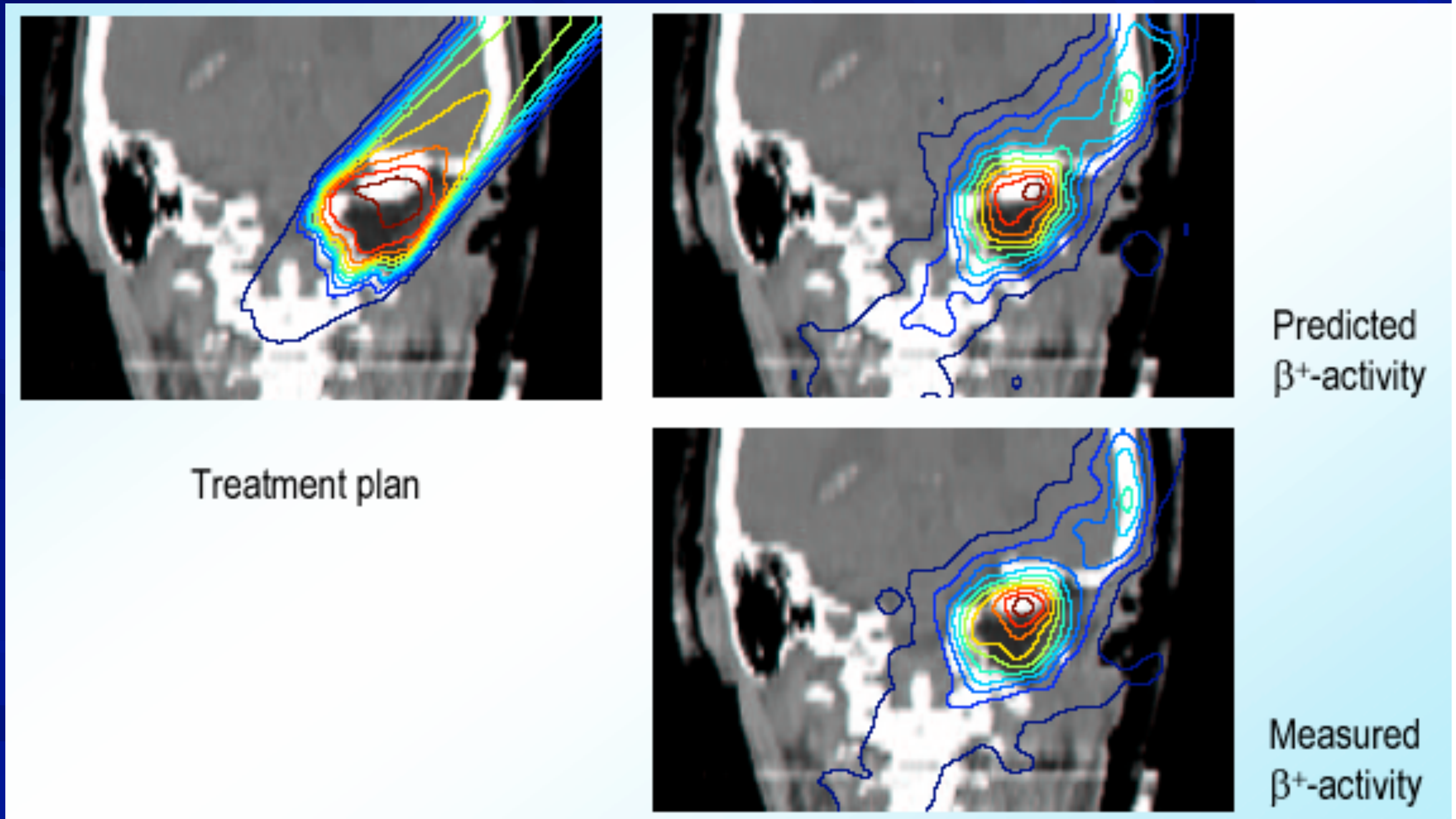


- Range verification for portal with high penetration depth and inhomogeneous target volume

Clinical results at GSI

- Range verification in delicate situations:
  - Stopping of the beam in front of organ at risk





Thanks to

- R. Lecomte (CHU Sherbrooke)
- P. Lecoq (CERN)
- R. Ferrand (CP Orsay)
- Prof. J.N. Talbot (Hôpital Tenon- Paris)
- J. Remilieux & M. Bajard - (ETOILE project)
- Prof J.P. Gérard (Nice)
- U. Amaldi (Pavia project)
- W. Enghardt & K. Parodi (FZR-GSI)
- M. Grossmann (PSI)
- W.W. Moses (LBL)
- C.Woody (BNL)
- R.Aymar (CERN) ....and many others